# FOREIGN REFERENCE PRODUCTS IN THE REGISTRATION OF GENERIC MEDICINES IN SOUTH AFRICA: A CASE STUDY

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# Abstract

**Introduction:**

Due to the increase in healthcare costs, generic medicines have been adopted for used in both developed and developing countries. When a generic or 'multisource interchangeable medicine' is to be registered, studies that prove that the generic is equivalent to the Innovator Product (IP) are used. The generic medicine is required to prove that it will mirror the IP in terms of safety, quality and efficacy and, in South Africa, the Medicines Control Council (MCC) ensures that generic medicines meet these requirements. Generic medicines may be registered using bioequivalence data obtained from comparison with a domestic reference product (usually the local innovator product) or in certain cases, a foreign reference product (FRP). The bioequivalence data can either be from *in vivo* or *in vitro* studies. The MCC guidelines require that for modified release preparations, *in vivo* bioequivalence studies are done for approval of registration; the exception being if a proportionally higher dose has already been registered. No information is currently given to prescribers and dispensers or to the public about whether a generic product was registered against a foreign or domestic reference product.

**Aims and Objectives:**

1.) To determine the number of generic medicines in a predetermined sample registered using a FRP as comparator and to document the transparency of pharmaceutical companies when approached to disclose information regarding the registration of these products.

2.) To describe and document the use of the Promotion of Access to Information Act (Act 2 of 2000) [PAIA] from the perspective of a 'layperson' in the context of medicines' regulation, in both private and public bodies.

**Methods:**

20 modified release and Biopharmaceutics Classification System (BCS) class IV products were selected from the 'generics dictionary' – a commercial publication – and letters were sent to the manufacturers of the products requesting information about the tests done to prove equivalence and whether they were performed against a domestic or foreign reference

product. The same information was also requested from the MCC. The requests were all made using the Promotion of Access to Information Act (PAIA).

**Results:**

Nine companies were represented by the 20 products chosen. Information was obtained about thirteen products. Ten of these products were registered using FRPs. Four products were registered based only on comparative dissolution studies. Four companies provided the requested information, two companies responded by refusing the requests and three did not respond at all. The MCC refused the request for information even after an internal appeal was lodged.

**Conclusions:**

The Promotion of Access to information Act was unsuccessful in obtaining information from the public body, and partly successful in obtaining it from the private bodies. While the title of the Act seems to indicate that the Act can be used to obtain information as such, it only provides for access to specified records. The MCC and the pharmaceutical companies involved in the study were under no obligation to provide the information as the request had not complied with PAIA requirements. The use of FRPs for registration is a reality in the pharmaceutical industry in South Africa. Neither the public nor healthcare professionals who prescribe medicines or who are involved in dispensing generic medicines as substitutes are aware of whether or not a FRP has been used to register a generic. Interchangeability cannot necessarily be guaranteed if the reference product was not proven equivalent to the local innovator product. It is debatable as to whether or not this information would be of any particular benefit to members of the public. Prescribers may choose to write 'no substitution' on their prescriptions if they were unconvinced that an FRP is acceptable. This could have consequences for healthcare costs. Dispensers are the most vulnerable in South Africa as they are obliged by law to substitute generic medicines when innovator medicines have been prescribed. Dispensers' views on the acceptability of the use of FRPs can be seen as irrelevant. In the end, as this study demonstrates, the only option in the present situation is to rely entirely on the MCC's rigour in assessing applications for registration of generic medicines.

This thesis is dedicated to my brother:

Alex Hwengwere

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# Abbreviations

| | |
|---|---|
| **AIDS** | Acquired Immune Deficiency Syndrome |
| **API** | Active pharmaceutical ingredient |
| **ADR** | Adverse drug reaction |
| **ALLSA** | Allergy society of South Africa |
| **ARV** | Anti retroviral |
| **ASA** | Advertising standards authority of South Africa |
| **AUC** | Area under the (plasma/serum/blood concentration-time) curve |
| **BCS** | Biopharmaceutics classification system |
| **CEO** | Chief executive officer |
| **CHRM** | Community for human resource management |
| **Cmax** | Maximum plasma concentration |
| **DCA** | Drug control authority |
| **DIO** | Deputy information officer |
| **DoH** | Department of Health |
| **DPP** | Dextropropoxyphene |
| **DRP** | Domestic reference product |
| **EMA** | European Medicines Agency |
| **EU** | European Union |
| **FDA** | Food and drug administration (of the United States of America) |
| **FRP** | Foreign reference product |
| **GMP** | Good manufacturing practice (or cGMP for current GMP) |
| **HCP** | Healthcare professional |
| **HIV** | Human Immunodeficiency Virus |
| **HVD** | Highly variable drug |
| **IP** | Innovator product |
| **IPR** | Intellectual property rights |
| **MARS** | Medicines and Related Substances Act |
| **MCAZ** | Medicines Control Authority of Zimbabwe |
| **MCC** | Medicines Control Council of South Africa |
| **MEC** | Minimum effective concentration |
| **MTC** | Maximum therapeutic concentration |

| | |
|---|---|
| **NAPM** | National Association of Pharmaceutical Manufacturers |
| **NDP** | National Drug Policy |
| **NOFSA** | National osteoporosis foundation of South Africa |
| **ODAC** | Open Democracy Advice Centre |
| **PAIA** | Promotion of Access to Information Act |
| **RNG** | Random numbers generator |
| **SA** | South Africa |
| **SAHA** | South Africa History Archive |
| **SAHRC** | South African Human Rights Commission |
| **SUPAC** | Scale-up and post approval changes |
| **TB** | Tuberculosis |
| **Tmax** | Maximum time taken to attain Cmax |
| **USA** | United States of America |
| **UK** | United Kingdom |
| **UN** | United Nations |
| **WHO** | World Health Organization |

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# Glossary

| | |
|---|---|
| **Action research** | Action research is a form of enquiry that enables practitioners to evaluate their research process and make decisions about the next steps on an ongoing basis during the research. |
| **Bioavailability** | Absence of a significant difference in the rate and extent to which the active ingredient or active moiety in two pharmaceutically equivalent products becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study |
| **Bioequivalence** | When two pharmaceutical products have bioavailabilities that are essentially the same in terms of peak Cmax and Tmax and AUC after administration of the same dose under the same conditions so that their effects with respect to both efficacy and safety can be expected to be essentially the same. |
| **Modified release preparation** | Dosage form for which the API release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms. |
| **Delayed release preparation** | Dosage form that releases an API(s) at a time other than promptly after administration. |
| **Extended release preparation** | Dosage form is one that allows at least a twofold reduction in dosing frequency or significant increase in patient compliance or therapeutic performance as compared to that presented as a conventional dosage form |
| **Pharmaceutical alternatives** | Medicines that contain the same active moiety but differ either in chemical form (e.g. salt, ester) of that moiety or in the dosage form or strength, administered by the same route of administration but are otherwise not pharmaceutically equivalent. |
| **Pharmaceutical equivalents** | Medicines that contain the same amount of active substances, in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route. |
| **Pharmacovigilance** | Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, management and prevention of drug related adverse reactions and effects or any others possible drug-related problems. |
| **Therapeutic equivalence** | Medicines that are pharmaceutically equivalent or alternatives and after administration in the same molar dose, their effect with respect to both efficacy and safety are essentially the same as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies. |
| **Transparency** | Frank, open or candid. Easily seen through, recognised, understood and clear. |

# List of Appendices

# Chapter 1: Introduction

## 1.0 Introduction

Medicines play a vital role in saving lives, restoring health, disease prevention and stopping epidemics. Governments and people therefore willingly spend money on them.[1] To add to that, medicines are the most widely used method of medical intervention and they are a cornerstone in the management of both chronic and acute diseases.[2] In Africa in particular, where access for vulnerable populations may be problematic, medicines may often be unaffordable, unavailable and unsafe due to poor quality.[3] The introduction and use of generic medicines has been noted as a breakthrough all across the globe. The use of generic medicines is being accepted and promoted from third world countries all the way to the first world countries.[4] The most important basis for the worldwide trust in medicines in general and more so for generic medicines is that they are of good quality, they are safe and effective and that their development, production, importation, exportation and subsequent distribution meets prescribed standards.[1] The bonus aspect about generic medicines is their cost. Generic medicines are cheaper and therefore present an opportunity for savings on medicines expenditure.[5,6] With that being said, the main goal of drug regulation is to guarantee the safety, efficacy and quality of drugs available to the public. Regulatory authorities are expected to observe a high level of efficiency, transparency and accountability as they carry out their function in drug regulation. This is essential currently so as to curb problems like the use of toxic, substandard and counterfeit drugs which are a waste of money and furthermore threaten the lives of consumers in both developing and developed countries.[1]

A great deal of research has been done on generic medicines. It ranges from consumer and healthcare professionals' acceptability and perspectives of the products to the actual processes involved for a product to eventually be registered as a generic medicine. Other researchers have looked at the possible negative aspects of generics and controversies that surround their use. Investigations have been made regarding their efficacy and quality in comparison to the Innovator or Brand name products. Queries have often been made and there have been efforts in assuring most of these are addressed from a regulatory and pharmaceutical industry perspective. The World Health Organization (WHO) has guidelines often adopted and modified by various countries to ensure generics are of a high quality and are safe.[7]

Eighty to eighty-six percent of the population of South Africa (SA) use the free public health facilities offered by the government for primary healthcare. If a cost is charged, it is often minimal.[3] This is of course in an effort to ensure access to and availability of medicines to the nation. The overall cost for the government to meet the healthcare needs of the nation is immense and the use of generics assists significantly in curbing the financial cost involved especially considering the prevalence of TB, HIV/AIDS and chronic diseases in SA.[3] For the procurement of medicines, the government promotes the use of generic medicines and works according to a public sector tender system which assists in lowering the cost.[8]

### 1.1 Motivation for research

Apart from ensuring that medicines that reach the consumers are of the appropriate standards in terms of safety, quality and efficacy, the role of the regulatory authority is also to provide appropriate and accurate information to the public.[1] The use of foreign reference products (FRPs) and comparative dissolution studies appear to be increasing in the registration of generic products in South Africa. The use of FRPs is permitted in the Pharmaceutical and Analytical guideline of the Medicines Control Council of South Africa (MCC).[9] Pharmaceutical companies must disclose the details of the reference product used to the MCC for purposes of registration. The information currently given to the prescribers, dispensers / pharmacists and the public about whether a domestic reference product (DRP) or a FRP was used for registration of a generic product is not provided by the MCC. Pharmacists are obliged by the Medicines and Related Substances Act, Act 101 of 1965 (Section 22F) to offer patients generic alternatives to prescribed medicines. The National Drug Policy 2006 (NDP) also states that 'Patients have the right to make informed decisions concerning their own health, including a choice for generic medicines.'[8] To make an informed decision, patients would need to be sure that the product they are receiving is of equivalent safety, quality and efficacy as the domestic innovator product (IP). It is also important for the prescribers and dispensers to have full confidence that the generic medicines that they are prescribing, dispensing and substituting have been proven to be equivalent to the local IP.

How and when the use of FRPs began is not clear. A senior member of staff, who has been involved in medicines regulation suspects that the use of FRPs as comparators may have stemmed from the apartheid era in South Africa when economic sanctions were imposed. It is assumed that an unintended consequence of sanctions was the continued suppression of the pharmaceutical manufacturing industry (amongst other industries) post-apartheid.[10,11] As South Africa had an active regulatory authority at that stage, the WHO did not push medicines through as they would do in countries that do not have an active medicines

regulatory authority. In contrast to that point of view it is noted that several multinational pharmaceutical 'giants' for example Novartis, Merck and Roche settled in South Africa during the apartheid era. One source claims that the industry flourished to such an extent that it became an economic pillar for the apartheid government.[12] Post apartheid, the use of FRPs seems to have remained a reality for the pharmaceutical industry. The use of FRPs as comparators in the registration of generic products is an area that has not been widely researched in South Africa, and is a key aspect of this study.

In considering the requirements that generic medicines are safe, effective and equivalent to the domestic IP, the use of the FRPs as comparators may compromise these requirements. As generic substitution is based on the concept on interchangeability, there are concerns whether products registered against a FRP are interchangeable with the local innovator product in clinical practice. There is ideally also a need for transparency about the use of FRPs from pharmaceutical companies who apply for registration of the new generic products, and from the regulatory authority that approves the registration of these products i.e. the MCC. The MCC is required to protect the public when it comes to medicines. It ensures that whatever is placed on the market has met acceptable requirements for safety, quality and efficacy.[13] This is consistent with the WHO requirements for regulatory authorities' duties.[1]

The pharmaceutical industry is one of the most profitable industries in the world. A financial motive drives it.[14,15] This may result in possible compromises on certain values.[14-16] The need for more affordable healthcare may also cause regulatory authorities and pharmaceutical companies to overlook certain critical issues in medicine registration, for example the tests used to ascertain the safety and efficacy of the drugs.[14] Multiple disasters have been recorded in history as a result of 'loopholes' in drug regulation. Examples include the death of 107 children in the United States in the 1930's because of sulphanilamide; the Thalidomide disaster in the 1960's that resulted in birth defects in children; and in India and Haiti multiple deaths were recorded as a result of medicines contaminated with diethylene glycol in the 1990's. Bringing it closer to home, in Niger 2500 deaths were recorded due to fake vaccines given for meningitis.[1] This shows the gravity and importance of effective drug regulation. Effective drug regulation is a tool that can tackle and possibly prevent such disasters.[1] This study looks at both the MCC and pharmaceutical companies and documents some issues concerning the requirements for proof of equivalence in generic medicines registration; as well as the use of FRPs.

## 1.2 Aims and Objectives

The Aim of the study is to investigate the use of FRPs in the registration of generic medicines in South Africa.

The objectives of the research include:

- To determine the number of controlled release and BCS Class IV products registered against FRPs in a predetermined sample of 20 multisource interchangeable (generic) medicines.
- To document the willingness of pharmaceutical companies to provide information about the registration of the selected generic products.
- To document the willingness of the MCC to provide information about the registration of the selected generic products.
- To describe and document the use of the Promotion of Access to Information Act, (Act 2 of 2000) from a 'laypersons' perspective in meeting the above objectives.

## 1.3 Layout of Chapters

Following this introductory chapter is a review of the literature (chapter two). The literature review gives a background to the research. It explains what generic medicines are, their importance and details regarding their registration locally and globally. It highlights local and global perspectives that patients and healthcare professionals have about generic medicines. The review also highlights controversies raised around generic medicines in the media and in pharmaceutical and scientific arenas. It gives an overview of methods involved in testing for equivalence and the guidelines set up to govern registration of these products. It discusses what foreign reference products are and their use in the registration of medicines. A history of the use of reference products and tests used in establishing equivalence of generic medicines in South Africa is given using a range of MCC documents. The chapter also addresses the concept of transparency and its application in the pharmaceutical industry. Details are provided about the Promotion of Access to Information Act and its use in obtaining information from both public and private institutions.

Chapter three describes the methodology. It describes and explains the methods chosen for use in data collection so as to achieve the aims and objectives of this study. It gives details as to how the data were collected in sequential steps for all the participants in the study.

The results are presented in chapter four. In this chapter, the communication between the investigator and the company correspondents is narrated. The chapter also describes how obstacles faced in the data collection were handled and overcome in line with the research methodology used. Due to a confidentiality agreement, no names of correspondents, companies and pharmaceutical products are disclosed.

The results are analysed, interpreted and discussed in chapter five. Finally chapter six gives a summary of the study and draws some conclusions. It also mentions limitations of the study and makes recommendations based on the findings of the research and literature. Possible future areas for study are suggested.

The researcher is also referred to as the 'investigator' in the dissertation. The terms generic medicines and multi-source interchangeable medicines are used interchangeably.

# Chapter 2: Literature review

## 2.0 Regulation of Medicines

In South Africa, the regulation of medicines involves overseeing a wide range of processes including development of products, manufacturing, clinical trials, registration, the use of unregistered medicines, post marketing surveillance, licensing of wholesalers and distributors, premises, people and practices, inspections of manufacturing facilities and distribution channels, product assessment and registration, adverse drug reaction monitoring and control of drug promotion and advertising. These are consistent with the WHO descriptions.[1,17] The term 'product' refers to new pharmaceutical medicines e.g. new chemical entities (NCEs) but also to generic or interchangeable multisource medicines. In some countries registration of medicines, which occurs in South Africa, is referred to as licensing or drug approval.[18]

## 2.1 Definition of a generic medicine

Generic medicines or interchangeable multi-source medicines are medicines that 'contain the same active substances which are identical in strength and concentration, dosage form and route of administration and meet the same comparable standards which comply with the requirements of therapeutic equivalence as prescribed.'[19] The WHO defines a generic product as a multisource pharmaceutical product which is intended to be interchangeable with the originator or other comparators. It is usually manufactured without a licence from the innovator company and marketed after the expiry of patent or other exclusivity rights.[20] The United States Food and Drug Administration (FDA) define a generic medicine as being a medicine that is identical or bioequivalent[1], to a brand drug in dosage form, safety and strength, route of administration, quality, performance characteristics and intended use.[3] Another less official but simpler definition of a generic is: '...a faithful imitation of a mature drug' which is intended to be interchangeable with the originator.[21] All the definitions of a generic product found in literature can generally be summed up by saying generics are copies of the original products meant to behave in a similar manner and produced after expiry of the patent by other manufactures.[4] The Innovator product (IP) or brand drug would be the drug the generic would be interchangeable with, and therapeutically equivalent to in clinical

[1] See glossary

practice. The bottom line is that the generic is not any better, nor any worse in any regard when compared to the IP.[22]

### 2.2 The use of generic medicines

The drive for generic prescribing and substitution globally has mainly been for financial reasons. The cost of healthcare has escalated all over the world and this is partly due to the increased cost of drugs.[3,4] Generic prescribing and substitution have been identified as a means of reducing the healthcare costs in South Africa and internationally, both in developing and developed countries.[4,23,24] The IP is more expensive compared to the generics due to the high cost of drug development in bringing a new product to the market. In 1987 this cost was estimated to be USD 114 million.[25] In 2006 the cost was estimated to be over USD 800 million with the cost of clinical trials contributing significantly to these figures.[15,25,26] In 2010, the Pharmaceutical Research Manufactures of America stated that it cost approximately $1 billion for a product to reach the market.[27] The cost of an IP is high so as to recover costs used in development, make a profit and re-invest in further drug development.[27-30] Figure 2.1 below shows a flowchart illustrating the drug development process. This process may take 10-20 years.[31,32]


**Figure 2.1: Drug discovery and development flowchart**[2]

Generic medicines can only be registered once the patent of the IP expires; and registration would normally require less time and less money.[29] All the preliminary work that happens prior to registration of a new product i.e. identifying a hit compound and lead compound, pre-clinical trials and the three phases of clinical trials are normally bypassed when generic medicines are registered.

[2] Summary of the drug development process constructed and adapted from: http://www.locumusa.com/pdf/handbooks/flow.pdf [Accessed 2011 November]

### 2.2.1 Increasing accessibility to medicines

The use of generics is particularly important in developing countries as they are more affordable to the population; but they're also important in developed countries like the United States of America (USA) and Europe.[2,23,33] Apparently many patients in the USA take less than the prescribed dose in efforts to make their medicines last longer. Some patients do not even buy the medicines because of inflated costs. Shifting to lower cost generics therefore has the potential to not only improve affordability and accessibility to medicines but also promote adherence.[2] Multiple chain pharmacies in the USA have adopted a $4 generic drug program which allows consumers to save money when purchasing their medicines monthly. The chain pharmacies, which include 'Walmart' and 'Target' make use of these low cost medicines in increasing affordability and access to medicines for low income patients and patients with chronic diseases.[2] A similar 'scheme' does not yet exist in South Africa.

In Kenya, where generic medicines make up to 90% of the medicines consumed, their Constitutional Court in 2008 barred the government from implementing the Anti-Counterfeit Act of 2008 as it also applied to generic medicines. The Act confused Intellectual property rights (IPR) and quality issues hence defining legitimate generic drugs as counterfeits.[33] Three petitioners protested that this legislature denied them access to affordable and essential medicines and the Judge agreed that the wording in the Act was 'rather vague' resulting in the confusion between counterfeit and generic medicines. The final ruling ensured that the importation and distribution of generic medicines in Kenya continued so as to maintain accessibility to medicines.[33]

## 2.3 How generic medicines reduce healthcare costs

Innovator drug companies generally try to make as much money as possible from their products before the patents expire and generic companies are permitted to apply for registration for that same product.[27] As the costs of generic medicine production and development prior to registration are significantly lower than those of the IP, this in part contributes to their lower prices. Not needing to conduct clinical trials significantly reduces the costs of development of generics. As patents expire, and other manufacturers make generics which compete for the market, a further lowering of prices occurs.[23,34] The IP itself is often forced to lower its price as well.[27]

## 2.4 South African healthcare system

South Africa has a two-tier healthcare system i.e. the private and the public sectors. The private sector is funded mainly by out-of-pocket spending and medical aid schemes while the public sector is funded mainly by the government. This is from general tax and other revenues.[8,35] South Africa's population was set at over 50 million in July 2011,[36] and the public sector caters for approximately 80-86% of these people, providing medicines for free or at a minimal charge at primary healthcare facilities.[6,8] In 2009, 5.6 million people were estimated to be living with HIV/AIDS in SA and a 2010 report from the United Nations (UN) still indicates SA as being one of the most severely affected countries in Southern Africa.[37,38] In addition, SA is one of the leading countries in the world with regards to TB infection.[39] In terms of chronic conditions: antihypertensives, hypolipidaemic agents and antidepressants were the three therapeutic groups contributing the most in terms of healthcare expenditure in 2004, 2005 and 2006.[35,40]

Considering the high prevalence of HIV/AIDS, TB and various chronic diseases in SA, providing free healthcare to such a large proportion of the population is a financial burden on the government. Despite this, it was noted that in 1990 the private sector was responsible for 80% of the country's total expenditure on drugs, while 60-70% of the total volume of pharmaceuticals was consumed in the public sector.[35] In 2006 the minority private sector consumed over half of the country's annual healthcare expenditure.[35] Generic medicines contribute in making the provision of free healthcare possible.[41] The generics industry has made medicines more affordable and hence more accessible to government and ultimately to individuals.[8,23,41]

The Department of Health (DoH) procures medicines via state tender schemes which are described in detail in the National Drug Policy of 1996 (NDP). To ensure cost effectiveness both national and international tendering is permitted. This allows the state to purchase in bulk and at a fixed price for set periods.[8,23] This system allows for price negotiations and once the contract is awarded and signed the provincial authorities make arrangements to get stock from the suppliers.[8] Preference is generally given to national tenders but regardless of that, international tenders will be considered in an effort to keep costs as low as possible.[8] The competition results in lower prices.

Several generic medicines manufacturers have been established in SA. Some of these are also distributors of products that have been manufactured elsewhere. Aspen Holdings, which is

one of the leading generic manufacturers in SA also distributes generic products acquired from India. In 2010, Aspen restructured its oncology joint venture with Strides Arcolab, an Indian pharmaceutical company. The joint venture entails that Strides would license its existing and future oncology products to Aspen to distribute.[42] India has emerged as the leading supplier of generic medicines to developing countries.[43] It has been observed that a significant quantity of generic antiretrovirals (ARVs) for developing countries are produced and exported from India. It is claimed that changes in the availability of generic medicines from India would affect both affordability and availability of medicines elsewhere.[43] Cipla Medpro South Africa Limited is another generics company which has an arrangement with Biomab, which in turn is a division of the Chinese pharmaceutical company Desano Pharma. The deal gives Cipla Medpro access to the biotech medicines developed by Biomab, including biosimilars and monoclonal antibody medications.[44]

### 2.4.1 Generic utilisation in South Africa

The National Association of Pharmaceutical Manufacturers (NAPM) has been on a drive to raise awareness with regards to the use of generic medicines here in South Africa. In 1996, a low rate of 13.9% was noted for generic substitution.[4] In 2003 NAPM believed that SA was still lagging behind in the use of generic medicines as they were making up only 20% of the volume of all prescriptions. The organisation believes that using more generics could save the country up to 24 million Rand.[4] In December 2006, the generic utilisation of SA in terms of volume had increased from 35.3% in December 2002 to 53.5%.[45]

In terms of financial gain, a study in 1990 indicated that a potential saving of between 9.9% – 59.7% ( mean 41.1%) was possible with generic substitution in SA. In 1996, further research observed that generic substitution could reduce medicine costs by a further 10%.[23,35] To promote the use of generic medicines, the 2003 amendment of the Medicines and Related Substances Act, Act 101 of 1965 (MARS) Section 22F[3] requires that Pharmacists **must** offer

[3] **22F Generic substitution**

(1) Subject to subsections (2), (3) and (4), a pharmacist shall-

(a) inform all members of the public who visit his or her pharmacy with a prescription for dispensing, of the benefits of the substitution for a branded medicine of an interchangeable multi-source medicine; and

(b) dispense an interchangeable multi-source medicine instead of the medicine prescribed by a medical practitioner, dentist, practitioner, nurse or other person registered under the Health Professions Act, 1974, unless expressly forbidden by the patient to do so.

(2) If a pharmacist is forbidden as contemplated in subsection (1) (b), that fact shall be noted by the pharmacist on the prescription.

patients generic alternatives to prescribed medicines.[19] Similar legislation has been adopted by various other countries across the globe including Finland, Japan and Iraq.[47-49]

The use of generic medicines was envisaged in the National Drug Policy (NDP) of 1996 as follows:

> **4.2 The use of generic drugs**
> The use of interchangeable multi-source pharmaceutical products (IMPP), using the international non-proprietary name (INN), or generic name, is a recommended step to reduce drug costs and expenditure. It also contributes to a sound system of procurement and distribution, drug information and rational use at every level of the healthcare system.
>
> - The availability of generic, essential drugs will be encouraged through the implementation of incentives that favour generic drugs and their production in the country.
> - The policy will aim at achieving generic prescribing in both the public and private sectors. Until this aim is achieved, generic substitution will be allowed, through legislation, in the public and the private sector.
> - It will be incumbent on the pharmacist, prior to dispensing a prescription, to inform the patient on the benefits of generic substitution and to ensure that substitution takes place with the patient's full understanding and consent.
> - Patients have the right to make informed decisions concerning their own health, including a choice for generic drugs.
> - A regularly updated list of products that cannot be substituted will be prepared and disseminated by the MCC.

In 2009, the Department of Health in the UK was also considering automatic generic substitution. This would mean that when a dispenser received a prescription with a brand name product, he/she would be free to substitute and dispense a generic version of the medicine.[50]

### 2.4.2 Global economic impact of generic utilisation

The European Union (EU) has estimated that generic substitution in their primary care systems will save £45million a year.[51] With a generic prescribing rate of 83% recorded in

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> (3) When an interchangeable multi-source medicine is dispensed by a pharmacist he or she shall note the brand name or where no such brand name exists, the name of the manufacturer of that interchangeable multi-source medicine in the prescription book.
> (4) A pharmacist shall not sell an interchangeable multi-source medicine-
> (a) if the person prescribing the medicine has written in his or her own hand on the prescription the words 'no substitution' next to the item prescribed;
> (b) if the retail price of the interchangeable multi-source medicine is higher than that of the prescribed medicine; or
> (c) where the product has been declared not substitutable by the council. (emphasis added)

2010, Europe has one of the highest rates of generic usage.[50,52] In 2009 Canada's healthcare system saved more than $4 billion through using generic prescription medicines.[41] In 2007, in the USA, 63% of all prescription drugs were generic medicines. Generic medicines save consumers and purchasers of these prescription drugs tens of millions of dollars per year.[5,53] Estimates from IMS Health[4] in the USA are that the US healthcare system, over the four years from 2011, will save at least $70 billion due to the replacement of brand name drugs by generics. However with the introduction of the Affordable Care Act extraordinary increases in brand name drugs, especially those with patents about to expire, have occurred.[27] The Japanese government strongly supports generic substitution as it was estimated it would reduce total drug costs by 1,3 Trillion JPY[5].[48] In Finland, where generics were introduced in 2003, consumers have the potential to save up to 60% if generic substitution is fully implemented.[47]

### 2.5 Consumer acceptability of generic medicines

In general while governments all over the world have welcomed generic medicines in terms of possible financial benefits, some consumers still have reservations regarding generic medicines. The common issues that are stated regarding generic medicines are as follows:

- Mistrust of the generics
- The lower prices are often associated with poor quality
- Lack of awareness regarding generics
- Claims of differences in safety, quality and effectiveness.[24,34,41,49]

#### 2.5.1 South Africa

A small case study conducted by third year pharmacy students in 2007 at Rhodes University on 23 university students, compared to 18 older individuals showed a lack of appreciation of the benefits of generic medicines among the older participants.[54] A study conducted on a national level in SA showed that the low cost of generics was often associated with perceptions of poor quality and they were generally treated with suspicion even when provided by the State.[6] '...This body does not want free medicines...' was one of the statements made by the participants. The study however also showed that informed patients were more likely to use generics.[6] The respondents in the study indicated that they would opt for generics if their medical practitioners, rather than pharmacists recommended the generic medicines as they trusted doctors more regarding generic medicine use.[6]

[4] A provider of information services for the healthcare industry

[5] Japanese Yen

### 2.5.2 Beyond South African borders

In 2008 Japan introduced a policy to encourage generic substitution. As in SA the policy allows a pharmacist to substitute prescribed medicines unless the prescriber strictly states a refusal for substitution. Elderly Japanese consumers were sceptical about generic medicines' safety and effectiveness.[48]. In Iraq, a study on patients' perceptions of generics showed a distinct lack of awareness of generic medicines among Iraqi consumers.[49] Some of the barriers to acceptance identified were a familiarity with the IP and an unwillingness to change, prescribers' inclinations to prescribing only IP and fear of counterfeit medicines.[49]

In Melbourne Australia, an additional problem cited which reduced acceptability of generic medicines was the occurrence of adverse drug reactions (ADRs) experienced by some patients when a change from an IP to a generic was made.[55] Certain generics were also reported to be causing problems on a customer advocacy website in the USA[6]. Most of the stories shared on the website were from patients who had been switched to a generic from a brand name or IP. Some experienced side effects while others found that the symptoms returned or became even worse compared to when they were not medicated.[56] In Portugal and Spain, acceptability of generic medicines was based on whether the disease condition was serious or minor[57] – a similar finding to that observed in SA.[6,49] Consumers in Germany displayed a general scepticism because of the lower price and consumers in Norway generally did not perceive the generics to be equivalent to the IP and hence did not trust them.[48]

### 2.6 Healthcare professionals' acceptance of generic medicines

The particular healthcare professionals referred to here are prescribers and dispensers. How prescribers and dispensers view generic medicines has an impact on the use of generics. It clearly influences prescribers' prescriptions and dispensers' substitution practices. They play a key role in promoting awareness of the use of generic medicines. Promotion of generics use by either the prescriber (doctor) or the dispenser (pharmacist) results in a greater acceptability of generic medicines.[6,48,49]

A third of New Zealand pharmacists in one study were unable to correctly define the term generic medicine. This study exposed that the pharmacists also thought that generic medicines were of an inferior quality compared to the branded products. The pharmacists echoed the lack of trust displayed by some consumers as they had had to deal with patients

[6] People's Pharmacy www.peoplespharmacy.com

experiencing ADRs after a generic medicine had been substituted for a brand medicine.[41] Clinicians from the Allergy Society of South Africa (ALLSA) and the National Osteoporosis Foundation of South Africa (NOFSA) have suggested that clinical trials be done to prove interchangeability between generics and brand name drugs.[58] In a Finnish study half the doctors involved expressed that not all interchangeable / generic medicines are safe.[47] A national survey in Malaysia identified a lack of confidence in substitution of branded products. It showed that pharmacists were more willing to make generic substitutions for mild to moderately serious diseases and not serious diseases.[59] Some cardiologists and neurologists in the USA expressed concern over generics as any slight changes could have potentially serious negative effects on the patients' health.[56]

The automatic generic substitution system that the Department of Health of the UK considered introducing in 2009 was criticised for possible clinical implications for patients. It was highlighted that generic substitution may have a negative impact on adherence, particularly for patients on chronic medication. Elderly patients often develop routines based on the appearance of their medication. Any changes can be confusing. The potential to disrupt patients' medication regimens, the potential for adverse reactions, and under-treatment in other individuals were all mentioned as reasons why generic substitution may not be ideal.[50]

### 2.7 The registration of generic medicines

The WHO states that all pharmaceutical products including multi-source products should only be used in a country after approval by its local authority.[20] For countries that do not have functional regulatory bodies, the WHO guidelines are often adopted for use.

#### 2.7.1 Basis for registration

For a generic medicine to be registered and put onto the market it has to show that it is of the same and appropriate standards of quality, safety and efficacy as the IP. Furthermore, reasonable assurance needs to be given that the generic is therapeutically equivalent and interchangeable with the IP.[18,20,22] This means that the generic medicine and IP contain the same amount of active substance, in the same dosage form, are intended for the same route of administration in the same molar dose and the effects they produce with respect to both efficacy and safety are essentially the same. The generic can therefore be interchanged with the IP in clinical practice.[18,20] The regulatory authority would be responsible for ensuring that products that get onto the market have met the appropriate standards.[1]

### 2.7.2 Interchangeability

Interchangeability is the basic concept that is used in generic substitution,[60] when one product can be used in the place of another and the same results can be expected. Ideally the one product would be the IP and the generic is registered by using the IP as a comparator. The two products are meant to mirror each other in therapeutic effect and efficacy, quality and safety.[22] Figure 2.2 below indicates the concept of generic substitution and interchangeability. The double-sided arrows in the figure below indicate interchangeability.

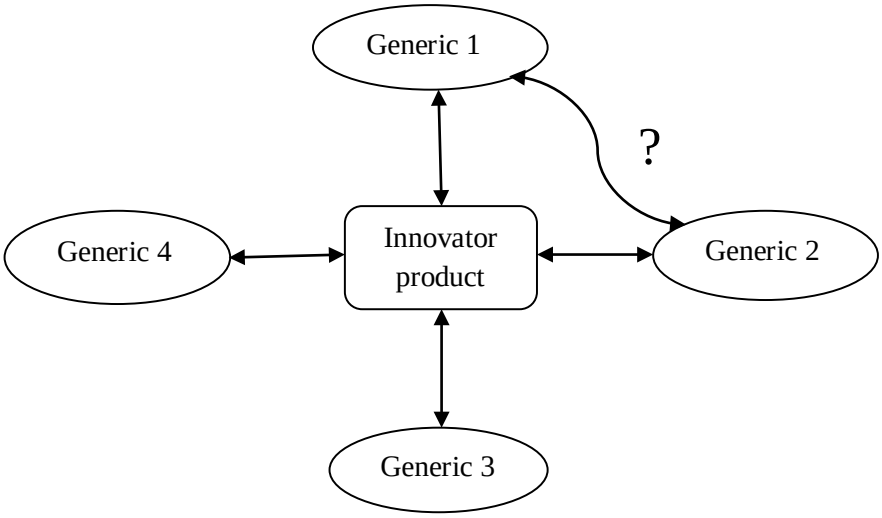


**Figure 2.2: The concept of interchangeability**[7]

### 2.8 The Medicines Control Council

The MCC is a statutory body established in terms of the Medicines and Related Substances Act, Act 101 of 1965.[61] The mandate of the MCC is to safeguard and protect the public through ensuring that all medicines that are sold and used in SA are, therapeutically effective, safe, and consistently meet acceptable standards of quality.[13,61] Companies apply to the MCC for registration of new products including multi-source medicines. The MCC requires applicants to show adequate evidence of safety, efficacy and quality. To facilitate this the MCC has prepared guidelines which are accessible from their website (www.mccza.com) to assist applicants in submitting appropriate data for registration.[62] Prior to the provision of these guidelines, the Registrar of Medicines used to publish circulars that were distributed to the stakeholders, and before that the Registrar and industry referred to what was commonly known as the 'blue book' which served as a common reference.[62]

[7] Adapted from: http://www.saudiannals.net/text.asp?2008/28/1/33/51758 [Accessed 2011 Dec 7]

### 2.9 Tests used in proving equivalence with the innovator product

There are *in vivo* and *in vitro* requirements that can be used to assure interchangeability of the generic medicine without compromising safety, efficacy and the quality of the pharmaceutical product.[63] While for some pharmaceuticals like parenteral formulations of high water content, Good Manufacturing Practice (GMP) and evidence of compliance with Pharmacopoeial specifications is sufficient to prove interchangeability, this is not the case for other dosage forms such as solid and liquid oral dosage forms. For these, more complex considerations would have to be made.[63] When the IP is registered it has gone through a long series of tests in animals and eventually clinical trials in humans.[18,28] Ideally, clinical studies would be performed to demonstrate whether or not there is equivalence between the IP and the proposed generic. This however requires a large number of participants and is financially daunting for the company wanting to register the generic. Therefore, when generic medicines are registered, clinical trials are not carried out. This not only conserves finances but also saves time.[18,25,58,63]

#### 2.9.1 Bioequivalence studies

Biostudies or bioequivalence studies have been an accepted standard in ensuring the therapeutic performance of medicines following manufacturing changes as well as for generic medicines approval.[18,64] Bioequivalence means that there is absence of a significant difference in the rate and extent to which the active ingredient or active moiety in two pharmaceutically equivalent products becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[63] The objective of bioequivalence testing is to quantify and thereafter compare the pharmaceutical performance of different formulations which are pharmaceutically equivalent.[62] The development of bioequivalence testing over the last 40 years has been critical to determining pharmaceutical and therapeutic equivalence. Experts in the science of bioequivalence testing, state that therapeutic equivalence can be assured when the multisource product is both pharmaceutically equivalent and bioequivalent, in which case it would be an alternative to the IP.[20] The WHO defines therapeutic equivalence as when two pharmaceutical products are pharmaceutically equivalent (or are pharmaceutical alternatives) and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are essentially the same, if administered to patients by the same route under the conditions specified in the labelling.[20] Pharmaceutical equivalents are products that contain the same molar amount of the same API, in the same dosage form, if they meet comparable

standards, and if they are intended for administration by the same route.[20] Products are pharmaceutical alternative(s) if they contain the same molar amount of the same API but differ in dosage form (e.g. tablets versus capsules), and/or chemical form (e.g. different salts, different esters).[20] In South Africa the concept of pharmaceutical alternatives was first officially introduced in draft Regulations to the Medicines Act in July 2011. These Regulations have not yet been finalised.

*In vivo* bioequivalence studies are done in healthy individuals representative of the general population in terms of age, sex and race. Usually ten or twelve participants are required for immediate release preparations and twenty for modified release preparations.[9,65] These studies measure the bioavailability of the test product and the reference product. The parameters analysed are maximum drug concentration (Cmax) and area under the curve (AUC). Figure 2.3 below indicates these two parameters. Blood samples are taken from the participants prior to taking the medicine. Further samples are taken at set time intervals after the medicine has been administered to determine the drug concentrations over time. A concentration vs. time profile can be constructed which will show the absorption, distribution and elimination of the drug. This profile also indicates Cmax and AUC.[18,62,63]

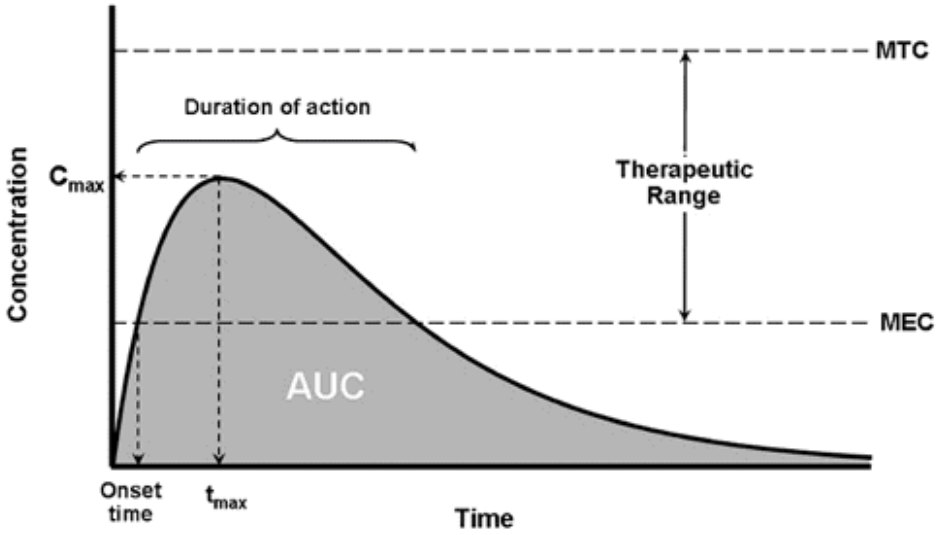


**Figure 2.3: A concentration-time profile constructed from bioavailability studies**[8]

Bioequivalence standards are based on the test and reference products producing the same plasma concentration-time profiles.[64] Bioavailability can be defined as the rate and extent to which the API becomes present at the site of action.[20] There are three types of bioequivalence studies. These are:

I. Fasting and single dose studies
II. Fed and single dose studies and
III. Fed and multi dose studies.[18]

For the registration of generic medicines, at least the fasting and single dose study is required.[18] Bioequivalence can therefore also be defined as when two pharmaceutical products have bioavailabilities that are essentially the same in terms of peak Cmax, Tmax and AUC after administration of the same dose under the same conditions.[65] In general, bioequivalence studies for modified release preparations may require testing in both fed and fasting states. This is to demonstrate the effect of food and therefore exclude the possibility of dose dumping.[65]

[8] This diagram is adapted from http://www.medscape.com/viewarticle/556234_4 MEC = minimum effective concentration; MTC = maximum therapeutic concentration

### 2.9.2 Dissolution studies

Dissolution research has being progressing for over 100 years. It began as a field in physical chemistry and has developed from there to applications in the pharmaceutical industry.[66] The process of dissolution aids in the physiological availability of the drug. *In vitro* dissolution testing is also used and may give sufficient evidence that there is equivalence between a proposed medicine and a reference product.[9,20,67] In pharmaceutical terms dissolution can be defined as the rate of mass transfer from a solid surface into the dissolution medium or solvent under standardized conditions of liquid/solid interface, temperature and solvent composition.[68] Dissolution testing is an important tool used in drug development and in the quality control of medicines.[63,66] Dissolution testing was initially developed as a quality control tool to ensure batch to batch reproducibility.[54,66,68,70] In a dissolution experiment, the volume of the dissolution medium is fixed and the agitation is provided by either of two devices, a rotating mesh basket, or a rotating paddle, USP I and II respectively.[63] The rate of rotation, volume of medium and temperature are parameters that are kept constant so that the analysis indicates purely drug release from the dosage form into the medium. Analysis of the dissolution medium is done as it is collected at set time intervals and a dissolution profile is constructed.[65,67] To mimic *in vivo* conditions, dissolution testing can be repeated by varying the pH of the dissolution media; acidic to more basic, pH 0.1, 4.5 and 6.8 (similar to the stomach and the small intestines). This gives an idea of drug release when the dosage form reaches those areas of the body.[65,67]

Figure 2.4 is an example of a dissolution profile. The y axis shows the percentage of the drug released and this is plotted against time on the x axis.

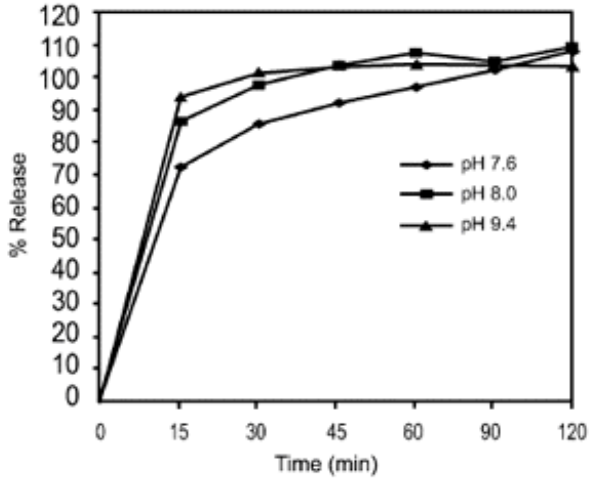


**Figure 2.4: A dissolution profile for tablets in various pH**[9]

[9] Diagram source: This diagram is adapted from the one provided at: http://www.scielo.br/scielo.php?pid=S0100-40422007000500031&script=sci_arttext

While figure 2.4 depicts a dissolution profile for one product in different pH media, dissolution profiles used in bioequivalence studies would compare the test and reference products. The dissolution profiles of the test and reference products are tested for similarities using the f2 similarity factor[10]. An f2 value of greater than or equal to fifty indicates that the two dissolution profiles are similar and that there is no need for further *in vivo* studies. An f2 value less than fifty indicates insufficient similarity and *in vivo* studies would be required. The exception to that general rule is when in both the test and reference products 85% or more of the API dissolves in less than fifteen minutes. In such a case, the similarity would be accepted without need for calculation of the f2 value.[67]

In general the applications for dissolution testing include evaluation and approval of scale-up and post approval changes (SUPAC) of registered medicines. The evaluation of proportionally similar dosage forms and *in vitro* testing for biowaivers is based on the Biopharmaceutics classification system (BCS).[65,66] Other studies have however indicated that similar dissolution profiles may be obtained for bio-inequivalent products. Dissolution testing is not a reliable prognostic tool of oral drug absorption (from the gastrointestinal tract into the blood stream) because a viable link has not yet been established between drug release from a formulation (or various formulations) and drug absorption.[66]

#### 2.9.2.1 Scale-up and post approval changes

After the registration of a medicine changes may be made in the manufacturing procedure or equipment, the site of manufacture and/or even the formulation. It is important to assess the effect of these changes on the quality, efficacy and safety of the products. Dissolution studies may be used under the specific conditions as a 'surrogate' method in assessing the impact of such changes.[67,71] The changes made to the registered pharmaceutical products are classified as either minor or major and designated as case A, B or C depending on the severity of the changes. The acceptance criteria applied to each case for the dissolution tests will differ.[18,67]

#### 2.9.2.2 Proportionally similar dosage forms

Dissolution testing may be used when two dosage forms are proportionally similar and the higher strength of the dosage form has already been approved.[65] A lower strength of the dosage form may be approved based on dissolution testing if the constituents of the dosage

[10] The similarity factor ($f_2$) is a logarithmic reciprocal square root transformation of the sum of squared errors, and is a measurement of the similarity in the percentage (%) dissolution between the two curves.

form i.e. the API and excipients are proportional. The manufacturer of the dosage forms and the site of manufacture must also be the same. An appropriate bioequivalence study should have been done on at least one of the dosage forms, preferably the higher strength.[65,67] For example, waivers of *in vivo* studies may apply to lower strength beaded capsules when the strength differs in the number of beads containing the API.[65]

#### 2.9.2.3 The Biopharmaceutics Classification System

The BCS is a scientific framework that classifies drug substances based on their aqueous solubility and intestinal permeability.[71,72] These two variables govern drug absorption.[64] The BCS was applied in practice by the introduction of waivers for *in vivo* bioequivalence studies/testing, and replacing these with comparative *in vitro* testing. The principle in the application of BCS is that if two similar medicinal products yield the same concentration profiles within the gastrointestinal tract following oral administration, they will lead to the same plasma profiles. Currently the MCC, FDA, EMA and WHO all refer to the BCS in their guidelines.[20,71,73]

The BCS classifies APIs into four categories:

- Class 1: High solubility and high permeability
- Class 2: Low solubility and high permeability
- Class 3: High solubility and low permeability
- Class 4:Low solubility and low permeability

**Table 2.1: Examples of APIs in the BCS classes**

| Class 1 | Class 2 | Class 3 | Class 4 |
|---|---|---|---|
| Chloroquine | Carbamazepine | Acyclovir | Taxol |
| Diltiazem | Danazol | Atenolol | Saquinavir |
| Metoprolol | Glibenclamide | Captopril | Ritonavir |
| Paracetamol | Ketoconazole | Cimetidine | Furosemide |
| Propanolol | Nifedipine | Metformin | Ellagic acid |
| Theophylline | Phenytoin | Neomycin B | Cyclosporin A |
| Verapamil | Troglitazone | Ranitidine | Coenzyme Q10 |

Class I APIs that are rapidly dissolving qualify for registration based on biowaivers and currently some class III products are also being assessed for inclusion into the group of APIs that can be exempted from *in vivo* bioequivalence studies.[64,72] The use of dissolution

testing assists in speeding up the process for drug approval and it is cheaper as compared to *in vivo* bioequivalence studies.[72]

### 2.10 Reference products

The tests used for the registration of generic medicines are all comparative. The product whose registration is being considered is tested against a reference product. The reference product is the one that the generic product is intended to be interchangeable with in clinical practice.[20] A reference product or comparator is a product that has been approved and has had its safety, efficacy and quality already established based on clinical trials. It is used as a standard against which the new product will be tested in either *in vivo* bioequivalence studies or *in vitro* comparative dissolution tests.[62] The suitability of a reference product is determined by the local drug or medicine regulatory authority.[20] The FDA compiled a list of comparators from which applicants can identify a reference product.[18] The WHO also has a list of comparators.[9]

#### 2.10.1 The domestic reference product

The reference product used as a comparator in these studies would ideally be the domestic reference product (DRP) or a local IP.[62,63] A product that was developed and is manufactured locally, having had its registration dossier submitted within the country in which the multisource product wishes to be registered would be a suitable DRP.[63]

#### 2.10.2 The foreign reference product

If the reference product is procured from another country it is called a foreign reference product (FRP). The Pharmaceutical and Analytical guideline of the MCC permits the use of FRPs.[9] There is no guarantee that the FRP's quality, safety and efficacy have been established through clinical trials. The information that is required to be furnished when a FRP is used for purposes of registration includes:

- The name and address of the manufacturer of the FRP
- The qualitative formulation of the FRP
- Copies of the immediate container label as well the carton or outer label of the FRP
- For modified release, evidence of the mechanism of modified release of the FRP
- The method of manufacture of the FRP if claimed by the applicant to be the same [as for the DRP]
- Procurement information of the FRP.[9]

## 2.11 Changes in MCC guidelines regarding use of reference products and tests used in establishing equivalence over the years

The sources of information used in this section include the 'blue book' (circa 1985 – used by the Registrars of Medicine and the Pharmaceutical Industry), circulars 14/89 of 1989 and 14/95 of 1995 and the MCC guidelines available on the website dated June 2007 and June 2011.

### 2.11.1 The blue book

The 'blue book' is in fact a file (with a blue cover) with the title: 'Guide to Medicine Legislation'. It was published by the Pharmaceutical and Chemical Manufacturers Association of South Africa – which no longer exists. The copy referred to in this study was obtained from a former Registrar of Medicines.

It contains the Medicines Act, its Regulations, certain MCC decisions, a marketing code and the Advertising Standards Authority's Code of Advertising Practice.

Chapter 5 of the 'blue book' outlines the requirements for registration of generic medicines.

#### 2.11.1.1 Tests involved in proving equivalence

The blue book uses the term 'pharmaceutical availability' to refer to the *in vitro* determination of efficacy and this is established through the use of comparative *in vitro* dissolution studies performed on a minimum of five specimens of the dosage form and if possible, the active raw materials in question. These dissolution studies were designated for single active ingredient formulations and were not intended for formulations with special release characteristics.[74] Comparative *in vivo* bioavailability studies were required in proving the efficacy of formulations with any special release properties e.g. sustained release preparations and combination formulations, both solid and liquid dosage forms unless specifically exempted. The Council could also require the provision of clinical data in addition to the bioavailability studies.[74]

#### 2.11.1.2 Choice of a reference product

The blue book makes a very bold and clear statement regarding the choice of a reference product:

> 'The innovator's medicine will be the only standard against which pharmaceutical availability and bio-availability studies will be measured. If the innovator's medicine is unregistered and

> significant differences are found, the Clinical committee will be approached for an option.'[74]

It then states that when identifying the reference products, the formulation needs to be similar and the product should already be registered in terms of the Medicines Control Act. (The Medicines Act was previously known as The Medicines and Related Substances Control Act.) In the event that a product with a similar formulation is not registered, a product acceptable to the Council could be used.[74]

### 2.11.2 Circular 14/89

Circular 14/89 was released on the 31st of December in 1989. The aim of the circular was to make stakeholders aware of how the policy had been modified about the required information and supportive data to be used as evidence of medicines efficacy when applying for registration. It superseded circular 4/86 and 1/88 which had related information.

#### 2.11.2.1 Tests involved in proving equivalence

In Circular 14/89, dissolution testing as a means of proving efficacy is mentioned as being suitable only for products that have the dissolution requirement included in the USP for single active ingredients or for a combination of active ingredients. In the event that the Council did not have any queries, such products' pharmaceutical availability data was sufficient in support of efficacy. The circular also states that pharmaceutical availability data may be submitted for vitamin and mineral combinations and multivitamins as long as the dissolution rate of the least water soluble vitamin plus one other vitamin was determined.[75] A list of active ingredients that required tests other than comparative dissolution studies was attached to the circular. See Appendix 1.

Comparative bioavailability studies are mentioned as a requirement for the assessment of efficacy for antibiotic and antibiotic combinations. Regarding general tablets, capsules, suspensions and suppositories, guidelines regarding bioavailability studies are given i.e. the number of subjects to be involved in the study.

> 'If bio-availability data are submitted for efficacy evaluation, at least ten experimental subjects are required in a crossover design and 20 subjects for long acting (slow release) preparations…'[75]

### 2.11.2.2 Choice of reference product

Again in Circular 14/89 the MCC boldly and clearly states that the reference product to be used in these comparative studies has to be the IP:

> 'The Innovator's product will be the only standard against which pharmaceutical availability and bioavailability studies shall be measures, whether the Innovator's product is registered or not, the only exception being multivitamins and vitamin and mineral combinations…'[75]

### 2.11.3 Circular 14/95

This circular was distributed on the 10th of February, 1995 titled 'Data required as evidence of efficacy in annexure 13'. It replaced circular 10/91. The circular deals with generic medicines and tests involved in proving efficacy.

### 2.11.3.1 Tests involved in proving equivalence

In Circular 14/95 eight options of tests are listed for use in proving efficacy depending on the relevance of the tests. These are, in order of appearance in the circular:

- Bioavailability
- Dissolution
- Disintegration
- Acid neutralising capacity
- Microbial growth inhibition zones
- Proof of release by membrane diffusion
- Particle size distribution
- Blanching test and
- any other method an applicant wishes to submit provided the rationale for submitting the particular method is included.[76]

When the circular discusses bioavailability studies, it lists instances in which bioavailability studies must be done as proof of efficacy for registration. One of those is when a modified release preparation or capsule e.g. slow and sustained release dosage form is being tested.[76]

The circular further discusses when dissolution tests can be used as proof of efficacy. The information given is similar to circular 14/89, the active has to have a USP requirement and the active should not appear on the list of attached active ingredients which required more

tests besides comparative dissolution studies. No other exceptions to dissolution testing are made besides the active ingredients listed and attached to the circular[11].[76]

#### 2.11.3.2 Choice of reference product

For a generic medicine, the choice of a comparator or a reference product to be used in comparative studies to prove efficacy must be a well-established innovator product. The choice of the IP must be justified by the applicant. In the case where the applicant seeks to register a product with different formulations, the product has to be compared with the product that was used in the clinical trial. In instances where there are major changes that have been done to the product that is being applied for, the product that was on the market prior to the changes was to be used as the reference.[76]

### 2.11.4 June 2007 MCC guidelines

The 2007 MCC guidelines referred to are the Pharmaceutical and Analytical, Dissolution and Biostudies. These documents were intended to be guidance for industry. The Pharmaceutical and Analytical guideline is an umbrella guideline for the quality of medicines. The Dissolution guideline describes how to conduct dissolution testing and the settings and specifications under which dissolution testing may be used as a quality control requirement and in support of a waiver for bioequivalence testing. The Biostudies guideline defines bioavailability and bioequivalence and explains when they will be required in order to prove safety and efficacy. Guidance is provided on how to conduct the appropriate studies and how the data acquired are to be evaluated. This guideline also indicates when *in vitro* instead of *in vivo* studies may be used.[77-79]

#### 2.11.4.1 Proof of efficacy

A similar list to that provided in circular 14/95 is given in the Pharmaceutical and Analytical guideline showing the available methods for proving equivalence and again, all the tests are meant to be comparative.[77] The Dissolution guideline describes dissolution as both a quality control requirement and as a ‘surrogate’ to bioavailability studies. The term bio-waiver is described, which depicts a scenario were *in vivo* bioavailability studies are waived and dissolution studies used to prove equivalence. Bio-waivers are only applicable if the active substance is highly soluble and should not cause any bio-availability problems.

[11] Appendix 1

In addition to that, the active substance must be in a dosage form that is rapidly dissolved in the physiological pH interval after administration.[78,79]

Bio-waivers are also permissible when different strengths of a registered product are being introduced.[65] The Biostudies guideline states that *in vivo* bioequivalence studies through pharmacokinetic bioavailability, pharmacodynamic studies or a comparative clinical trial are especially important when dealing with drugs where there is a risk of possible differences in bio-availability which may result in therapeutic inequivalence. An example given is in the registration of modified release pharmaceuticals designed to act by systemic absorption.[79]

### 2.11.4.2 Reference products

In 2007 the MCC recommended that the reference product should preferably be a locally procured product. In the event that there is more than one product that qualifies as a reference product, the market leader should be used as long as proof was provided of market leadership. The Pharmaceutical and Analytical guideline goes on to give four options regarding reference products, in order of preference:

(i) the innovator product registered and procured in South Africa; or

(ii) the innovator product for which a marketing authorization has been granted by the health authority of a country with which Council aligns itself (see General Information guideline 3.1.4), and which is to be purchased from that market, or

(iii) a product from the latest edition of the WHO International comparator products for equivalent assessment of interchangeable multisource (generic) products QAS/05.143. [http://www.who.int/medicines/services/expertcommittees/pharmprep/QAS05_143_Comparator] The primary manufacturing site is indicated in the WHO comparator list, and the comparator is to be purchased in that country, or;

(iv) in the case that no innovator product can be identified – within the context of (i)–(iii) above, the choice of the reference must be made carefully and must be comprehensively justified by the applicant.[77]

A note is given below this list:

> '...a product that is approved based on comparison with a non-domestic reference product may or may not be interchangeable with currently marketed domestic products.'[77]

The choice of the reference product also needs to be justified by the applicant and details regarding the country from where it is procured are to be provided.[77]

### 2.11.5 June 2011 MCC guidelines

The June 2011 guidelines are mostly similar to the June 2007 guidelines. Additional information is given in the Biostudies guideline about the requirements needed if a foreign reference product is used as the comparator.[65]

The guidelines inform applicants that the choice of reference product can be made by the applicant and a sufficient justification must be provided. The provision for use of a foreign reference product is made. This may be a product registered in South Africa but procured in a country with which the MCC aligns itself with.[9]

Table 2.2 below is a summary of the changes over time in reference product choice and tests required to prove equivalence derived from the MCC documents referred to.

**Table 2.2: Changes in the MCC guidelines over the years**

| | Blue book | Circular 14/89 | Circular 14/95 | June 2007 | June 2011 |
|---|---|---|---|---|---|
| **Tests to prove equivalence** | Bioavailability studies for all modified release.<br>Dissolution for single active ingredient preparations only | Bioavailability studies for all modified release.<br>Dissolution accepted for combination ingredients. List of exceptions | Bioavailability studies for all modified release.<br>Dissolution can be used except for listed exceptions | Bioavailability studies for all modified release except when bio-waiver applies | Bioavailability studies for all modified release except when bio-waiver applies |
| **Choice of reference product** | Only Innovator product | Only Innovator product | Innovator product and choice to be justified | Four choices including FRP | Four choices, including FRP |

### 2.12 Controversies surrounding the use of generic medicines

There are various controversies about the use of generic medicines. Concerns, views and perspectives raised by consumers and healthcare professionals have already been mentioned. The following issues are raised by academics, scientists and researchers. They look at generic medicines from a more scientific and pharmaceutical perspective.

### 2.12.1 Differences in content

As much as the generic medicine contains the same API as the IP, the chemical form may be different i.e. another salt or ester of the API. Two different salts of the same compound may not be identical and may exhibit different solubilities and absorption characteristics. This becomes problematic as dosages may often be expressed as the weight of the salt rather than the weight of the actual API.[51] Besides that, though the salts may be tested and proven to be bioequivalent, therapeutic equivalence also refers to the same safety and efficacy. When different salts or esters are used the stability and toxicity of the products may change.[80] Polymorphism is also a concern when it comes to the API. Quality release and stability testing can become problematic as a result of a change in polymorphic forms of the API. For example, Norvir®, which is a brand of semi-solid ritonavir in capsules, went onto the market in 1996 and in 1998 the drug began to precipitate in the capsule. The form I of the drug had converted to form II.[81] As polymorphism affects dissolution and drug absorption in the gastro intestinal tract, it is important to ensure the manufacturing and storage procedures maintain the desired polymorph.[80,81]

Mebendazole, which is a widely used anti-helminthic has three polymorphs, A, B and C the preferred being C. In 2002 a study on the ability of dissolution testing to distinguish between the different polymorphs was done and one of the conclusions made was that it was critical for importers of Mebendazole to import the correct polymorph as various generics were on the market. They also identified that the removal of sodium lauryl sulphate from the dissolution medium was one method of identifying between the polymorphs.[82]

In terms of content, the excipients used i.e. stabilising, bulking, sweetening, colouring and flavouring agents may also vary between products. This could possibly provoke not only allergies or intolerance but also result in serious adverse drug reactions.[29,51] In 2007, GlaxoSmithKline (GSK) introduced a new formulation of levothyroxine which contained different excipients compared to the originator product onto the market. The new product caused weight gain, lethargy and visual disturbances and in just over a year, 746 adverse reactions had been reported in New Zealand alone.[41]

### 2.12.2 A normal and healthy population

*In vivo* bioequivalence studies are performed in a ‘normal and healthy’ population.[20,73] The assumption that, if bioequivalence is exhibited in a normal and healthy population this

will equate to comparable tolerability and clinical efficacy in a patient (i.e. sick) population, has not been established as fact.[50,83]

### 2.12.3 Inter-ethnic variability

Due to genetic polymorphism in individuals' drug-metabolizing enzymes, there is a high degree of variability in drug metabolism among populations.[73,84] Differences in ethnic groups may result in significant differences in the ability to metabolise certain drugs.[84-87] The enzymes of the cytochrome P450 family play a key role in the metabolism of various drugs. Genetic variations among different ethnic groups result in genetic polymorphism and the same enzyme may be expressed differently in different ethnic groups.[84] The cytochrome (CYP) enzymes can have significant differences between the following subfamilies CYP2D6, CYP2C, CYP3A, CYP1A2 and CYP2A6 in Caucasians and East Asians.[84]

CYP2D6 which metabolises generally lipophilic drugs has over 80 variants. A study done analysing the differences in the pharmacokinetics of certain drugs amongst East Asians and Caucasians indicated that the Asians required less neuroleptic medication compared to the Caucasians. The metabolism of codeine also shows significant differences between ethnic groups.[84] A product tested in and approved for a particular ethnic group may not perform equally well in a different ethnic group. Countries in the European Union (EU), Japan and the USA identified this as a problem.[88] Ethnic differences resulted in altered safety, efficacy, dosage and dosage regimens of drugs and this caused a reluctance to use foreign clinical data in the registration of drugs. To resolve this problem, the countries came together and drafted a set of guidelines that facilitated use of foreign data in an effort to minimise on the tests involved in drug approval.[84,88] This is how the 'International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use' (ICH) guidelines were developed.[88] In Africa similar efforts have been initiated to harmonise the pharmaceutical industry and regulation in an effort to increase speedy access to medicines, improve public health and ensure provision of high quality and effective medicines for the treatment of priority diseases.[89,90] The harmonisation would also involve the development of uniform guidelines for use within the countries participating in the harmonisation and ultimately lead to cost saving benefits for these participant countries. [89,90]

### 2.12.4 Universal bioavailability limits

There is a different understanding of the term bioequivalence from country to country. The Latin American countries; Bolivia, Columbia and Peru insist that bioequivalence testing involve clinical trials in human beings. They consider other tests such as dissolution testing and other *in vitro* testing insufficient to classify a product as a generic.[91] On the other hand Brazil and Argentina register a product as a generic if it has the same active ingredient as the IP, regardless of the tests done to prove bioequivalence.[91] The parameters assessed in bioequivalence studies are AUC and Cmax. Limits are set for these two parameters at a 90% confidence interval. In SA the limits for AUC are 0.8 to 1.25 and for Cmax it's 0.75 to 1.33. These limits are consistent with those of most countries, for example Canada, USA and Australia, except that the Cmax values in SA are wider than the 0.8 – 1.25 set for those countries.[63] Table 2.3 below shows AUC and Cmax values from different countries and those recommended by the WHO.

**Table 2.3 Limits for Cmax and AUC in various countries**

| Country | Limits for AUC | CI | Limits for C max |
|---|---|---|---|
| USA | 0.8-1.25 | 90% | 0.8-1.25 |
| Canada | 0.8-1.25 | 90% | 0.8-1.25 |
| Europe | 0.8-1.25 | 90% | 0.8-1.25 |
| | HVDs 0.8-1.25 | 90% | 0.8-1.25 |
| Australia | 0.8-1.25 | 90% | 0.8-1.25 |
| | HVDs 0.75-1.33 | 90% | 0.8-1.25 |
| WHO | 0.8-1.25 | 90% | 0.8-1.25 |
| India | 0.8-1.25 | 90% | 0.8-1.25 |
| South Africa | 0.8-1.25 | 90% | 0.75-1.33 |
| | HVDs scaled 0.80-1.25 | 90% | Scaled 0.75-1.33 |
| | HVDs 0.70-1.43 | 90% | 0.8-1.25 |

HVDs are highly variable drugs. These are drugs where the within-subject % coefficient of variation (%CV) of Cmax and/or AUC is greater than 30%. The wider limits for Cmax in SA were due to a special dispensation due to some unspecified difficulty in identifying Cmax.[63]

### 2.12.5 Lack of equivalence

Various reports regarding the lack of equivalence of the generic medicines to the IP have been made. An independent laboratory in the USA testing the equivalence of an original product of budeprion vs. the generic version showed different dissolution rates.[56] Budeprion is an antidepressant available as a modified release preparation.[92]

The generic version released the drug at a significantly faster rate than the IP, which may have accounted for the various side effects people had been reporting.[56]

Nifedipine is an anti-hypertensive drug which is also used in the treatment of chest pain due to coronary artery spasm. It is available under the names Adalat®, Nifedical® and Procardia®. In 2008, the NAPM complained to the Advertising Standards Authority (ASA) as questions had been raised regarding the equivalence of generic nifedipine to the IP. At least two of the generics that had been tested had failed to prove bioequivalence. The NAPM complained that there had been a misinterpretation of facts and that the studies done were not relevant to the SA market as they related to testing in Europe for a European market. The ASA dismissed the complaint as Bayer, the manufacturer responded by stating that no information was available in SA regarding nifedipine and hence facts from Europe had been used.[93] It must be noted that the ASA dealt only with the advertising claims made for these products as it does not have the regulatory authority to rule on the correctness of the registration of medicines.

Anti-seizure drugs are particularly problematic in the area of generic substitution. Some healthcare professionals argue that generic anti-epileptics are not equivalent to the brand name agents.[83,94] A survey of over three hundred neurologists indicated that 169 of 289 respondents reported breakthrough seizures in their patients with generics; and 163 of 291 reported an increase in adverse events on switching to a generic anti-seizure agent. Substitution of agents with narrow therapeutic ranges was identified as problematic; phenytoin, in particular, not only has a narrow therapeutic index, but also displays non-linear pharmacokinetics.[83]

## 2.13 The Promotion of Access to Information Act

South Africa and Zimbabwe were the first two countries in Southern Africa recognised to have legislature regarding access to information.[95] The Promotion of Access to Information Act, Act 2 of 2000 (PAIA) in South Africa was introduced in March 2001 and amended in February 2002.[96]

### 2.13.1 The purpose of PAIA

The PAIA was introduced after it had been recognised that the system of government in SA prior to April 1994 had resulted in a secretive and unresponsive culture in both public and private bodies. The apartheid era was characterised by segregation, secrecy and oppression which often led to abuses of power and human rights violations.[96,97] After 1994, one of the goals of the new government was to be transparent and accountable in an effort to be regarded as credible by the people of South Africa. The right of access to information was included in the Bill of Rights within the Constitution of South Africa[12]. Section 32 protects the right of access to information as a fundamental right.[97,98]

PAIA attempts to foster and encourage a culture of transparency in both public and private bodies. It serves to promote a culture in which the people of South Africa have the ability to gain access to information so they may fully exercise their rights.[95-97] To enable the people to do this the South African Human Rights Commission (SAHRC), a so-called 'Chapter 9 Institution' created by statute in Chapter 9 of the Constitution, was given the mandate to compile simple and easily comprehensible guidelines on how to use the PAIA. The SAHRC was also to be responsible to ensure that state institutions and private bodies developed PAIA 'manuals' in accordance with Sections 10 and 51 of the Act, and that these manuals were available for public viewing.[96,98] The SAHRC also promotes the use of PAIA to the public in collaboration with organisations such as the South African History Archive (SAHA) and the Open Democracy Advice Centre (ODAC).[99]

### 2.13.2 The challenges surrounding PAIA

PAIA is regarded as an underused Act. Ordinary members of the public have been identified as being generally unaware of the PAIA and their right and ability through it to obtain access to information. A report by the National PAIA Civil Society Network indicates that although the use of the PAIA has been increasing, the substantial failure of information holders to respond has rendered the requests 'futile'.[100] In a report compiled discussing the implementation of PAIA in the first ten years after its implementation, it was noted that many responses given to PAIA requests were blanket refusals with inadequate justification.[101] Officials in state institutions have also displayed a lack of awareness of the Act. This general lack of education and awareness surrounding the Act is a concern, and the ODAC, SAHRC and other organisations have made efforts to increase awareness by hosting workshops,

[12] The constitution of the Republic of South Africa, 1996 (Act 108 of 1996).

conferences and distributing leaflets about the PAIA.[96,100,102] The National PAIA Civil Society Network (PAIA CSN) is a collaboration of individuals and organisations that promote PAIA, and work towards achieving the desired openness and accountability that the Act represents.[99]

Another challenge regarding the full implementation of PAIA is the procedure involved in resolving disputes that may arise in the event that a request for information is denied.[102] An Internal Appeal process is available for public institutions. In this a requester may ask for a decision regarding a refusal to a request to be reconsidered. In the event that a request is denied after an internal appeal the matter would have to be taken to court.[96] In private institutions, there is no internal appeal structure and the only recourse available to a requester in the event of a refusal is to approach the courts.[96] Due to the expense and cumbersome nature of arranging court cases, implementation of the Act may be compromised.[102] Initially, PAIA cases were dealt with primarily in the High Court. In an effort to increase the enforcement of the Act, Magistrates are being trained in its use. Poor records management also presents a challenge as records were found to be not easily accessible.[100] The challenges of course do not compare to what was probably the greatest of them all: the breaking of the secretive culture that had developed during apartheid. Some attitudes and practices continue to manifest a lack of openness.[100]

A pre-PAIA court case, *Korf v Health Professions Council of South Africa* highlighted how effective the PAIA might eventually be without having to resort to the courts. In this case, the applicant requested hospital files in order to institute legal action against a medical practitioner.[103] The request was made in terms of Section 32 of the Constitution[13]. It was denied by the hospital as the records had been passed on to the Health Professions Council of South Africa (HPCSA) for a disciplinary proceeding. The HPCSA refused access to the documents on the grounds that they were confidential. The court however decided in favour of the applicant.[103]

### 2.13.3 PAIA in the private sector

A private body is defined in the Promotion of Access to Information Act as:

> (a) a natural person who carries or has carried on any trade, business or profession, but only in such capacity;
> (b) a partnership which carries or has carried on any trade, business or profession; or
> (c) any former or existing juristic person, but excludes a public body.[97]

[13] Access to Information clause

Section 51 of the PAIA indicates that the head of a private body must establish a PAIA manual within six months of establishment of the body:

> **Manual**
> **51.** (1)Within six months after the commencement of this section or the coming into existence of the private body concerned, the head of a private body must compile a manual containing—
> *(a)* the postal and street address, phone and fax number and, if available, electronic mail address of the head of the body;
> *(b)* a description of the guide referred to in section 10, if available, and how to obtain access to it;
> *(c)* the latest notice in terms of section 52(2), if any, regarding the categories of record of the body which are available without a person having to request access in terms of this Act;
> *(d)* a description of the records of the body which are available in accordance with any other legislation;
> *(e)* sufficient detail to facilitate a request for access to a record of the body, a description of the subjects on which the body holds records and the categories of records held on each subject; and
> *(f)* such other information as may be prescribed.
> (2) The head of a private body must on a regular basis update the manual referred to in subsection (1).
> (3) Each manual must be made available as prescribed.
> (4) For security, administrative or financial reasons, the Minister may, on request or of his or her own accord, by notice in the *Gazette*, exempt any private body or category of private bodies from any provision of this section for such period as the Minister thinks fit.[97]

When a request is made to a private body, the application must indicate that it is protecting or exercising a particular right.[97,102] It is argued that this requirement often discourages the public from using PAIA to request information from private bodies. The Companies Act of 2008 is another statute which encourages accountability and transparency in the private sector.[102]

### 2.13.4 PAIA in the Public sector

Like private bodies, public bodies are required to have PAIA manuals. A public body is defined by the Act as:

> (a) any department of state or administration in the national or provincial sphere of government or any municipality in the local sphere of government; or
> (b) any other functionary or institution when—
> (i) exercising a power or performing a duty in terms of the Constitution or a provincial constitution; or
> (ii) exercising a public power or performing a public function in terms of any legislation.[97]

A report compiled in 2007 indicated that only 40% of government institutions had developed the PAIA manuals.[100] In general obtaining information from public bodies is problematic.

Some public bodies do not have deputy information officers who are responsible for responding to the requests as mandated by the Act.[100] To add to that, a clear protocol may not be in place regarding the PAIA in public bodies, and often when a request is received there is a reluctance to furnish the information. Only 36% of government institutions had a system for handling information requests in 2007.[100]

The PAIA CSN from 01 January to 31 July 2009 submitted various PAIA requests to public bodies at national, provincial and municipal levels. Only 12.7% of those requests received responses within the stipulated 30 days. At the end of the seven-month period, 34.5% of the requests had been responded to in full. For the remainder, the information was pending – either the decision of an internal appeal or litigation.[100]

### 2.13.5 Transparency

Transparency can be defined as 'The condition of being transparent', meaning having the capacity to allow light to shine through, being frank, open, candid and ingenuous. It encompasses being easily seen through, recognised, understood, obvious and clear.[104] The Business dictionary gives four definitions for transparency, one of which is: 'An essential condition for a free and open exchange whereby the rules and reasons behind regulatory measures are fair and clear to all participants'.[105] Transparency means there is visibility into a company's functions and activities for all stakeholders. The company would be acknowledging that its actions affect the stakeholder and transparency increases the stakeholders' confidence in the company.[106] It leaves room for recommendations and in various way improves the performance of the business.[106]

Transparency in the pharmaceutical context includes clinical trials and pricing and profits. In terms of clinical trials, various scandals have been reported in the pharmaceutical industry in the USA and European Union countries that resulted in a distrust of the industry by the public.[107-109] The fair and uniform disclosure of information is generally encouraged when clinical trials are done. Selective disclosure of information was reducing the credibility of pharmaceutical firms.[107,108] Methods have been developed by the EMA in an effort to allow the public to have access to otherwise confidential information. Representatives from patient and healthcare professional groups have been appointed as members of the management board of the EMA in an effort to empower the public. This level of transparency allows the public to know the reasoning behind certain decisions.[109] It also allows them to voice their opinions on policies and strategies regarding decision making around disease states. This allows for consistency and openness and the system in which 'patients and HCPs

do not understand because someone else understands for them' is abandoned. The EMA went as far as making assessment reports for the authorisation of new medicines available to the public.[109]

# Chapter 3: Methodology

### 3.0 Introduction

The study is framed as a case report using an 'Action Research' methodology. This chapter elaborates on Action research and its use in data collection for the study. Due to the cyclic nature of the action research approach, certain aspects of the unfolding methodology are presented in the results section, chapter four.

### 3.1 Action Research

Action research was first defined by Kurt Lewin, a social psychologist. Lewin described a form of research that not only identified the problems but included mechanisms for addressing the problems.[110] Action research is a form of inquiry that enables practitioners to investigate and evaluate their work in an ongoing fashion. It has also become increasingly popular as a means of professional learning. Action research provides researchers a mechanism to conduct research from a more involved (participant) point of view as compared to the more commonly used 'spectator' approach.[111] Participatory action research (PAR), which is a branch of action research, has been used in healthcare to solve problems in communities, thereby making sound contributions to the mainstream healthcare arena and nursing practice.[112]

Koch and Kralik believe that by working together with all stakeholders, participatory action research is a vehicle for making a difference in people's lives.[112] This type of action research is said to raise consciousness, produce knowledge and implement actions which empower people. The aim of action research is to result in improvements after a problem has been identified. The improvements involve the participation of 'practitioners' and the 'target' communities specific to the situation. Various means are used to generate data in action research ranging from observation, interviews and participants' written accounts.[110]

The 'spectator' (observer) approach which is often adopted in social research asks questions like; *What are those people over there doing? How can we understand and explain what they are doing?* This usually occurs when an outsider is conducting the research. When an insider is doing the research, the questions differ and become: *Is our work going well? How do we improve it where necessary?* This form of insider research can be taken further to a highly individual and personalised level. The questions asked become *What am I doing? What do I need to improve? How do I improve it?*[111] Three words form the basis for action research:

‘Look, Think and Act’. In its cyclic nature, action research promotes reflection and reconstruction.[112]

Action research often makes use of an action-reflection cycle shown as figure 3.1. The action-reflection cycle is a disciplined and systematic approach to research and the steps involved would often be:

- To take stock of what is going on.

  In this study, determining the current situation about the registration of generic medicines in South Africa, and what’s been documented in literature.

- Identification of a concern.

  The concern identified was the apparent use of FRPs to register generic medicines, possibly based only on comparative dissolution studies. Prescribers, dispensers and consumers are not informed about the comparators or tests used to register generic medicines. These concerns, and whether the ‘stakeholders’ should be informed, contributed to the research question.

- Thinking of a possible way forward.

  The investigator considered means of an initial pilot determination of the use of FRPs and of the tests used to prove equivalence. A plan of action was devised. The use of the PAIA was identified as a instrument which could provide the information.

- Trying it out.

  Requests were sent to the identified stakeholders.

- Monitoring the action and gathering data.

- Evaluating progress.

  Judgments about the validity of the data.

- Modifying practice in the light of the evaluation.

  Repeating the cycle with changes if necessary.

  If an acceptable outcome is not achieved, the process would be modified and the cycle repeated until the results are deemed satisfactory.

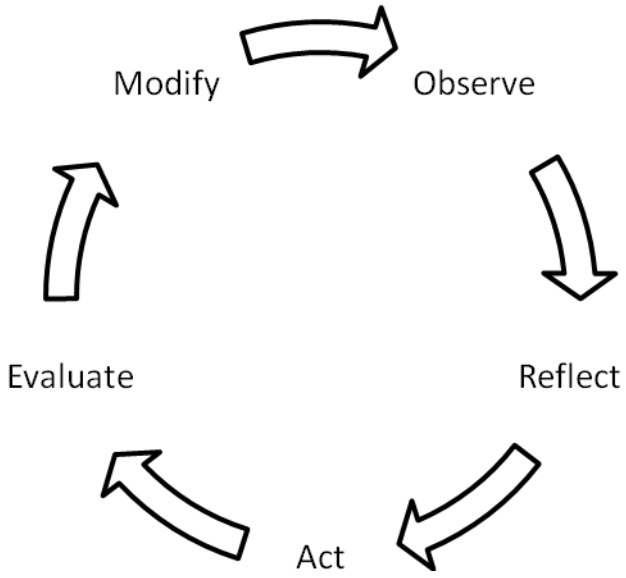


**Figure 3.1 Action-reflection cycle**[14]

### 3.2 Research Context

> 'Action research is a participatory, democratic process concerned with practical knowing in the pursuit of worthwhile human purposes . . . It seeks to bring together action and reflection, theory and practice, in participation with others, in the pursuit of practical solutions to issues of pressing concern to people and more generally the flourishing of individual persons and their societies'.[112]

This statement highlights certain key aspects of action research displayed in this research. The investigator is a trained pharmacist and the research is within her scope of practice. It is linked to her profession from a pharmacovigilance[15] perspective. The investigator took a stance of the MCC and pharmaceutical companies being partners in healthcare provision, along with prescribers, dispensers and other healthcare professionals who were not directly involved in the study. The key action research questions used for the study were: 'Is our work going well? In particular, is the current method for the registration of generic medicines the best possible? If not, how do we improve it where necessary?'

### 3.3. Case study format

This research was carried out as a pilot study in a case study format. As a case study, it involves a process of research and recording of developments relating to a particular

[14] Action-reflection cycle adapted from McNiff and Whitehead 2006[111]

[15] Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, management and prevention of drug related adverse reactions and effects or any others possible drug-related problems. WHO. The Importance of Pharmacovigilance. 2002.

individual or small group or institution.[104] The definition of case study more specifically describing this study is:

> "…the collection and presentation of detailed information about a particular participant or small group, frequently including the accounts of subjects themselves…" [113]

The emphasis in this study is exploration and description through use of the action research tool.

### 3.4 Ethics clearance

Prior to the collection of the data, the ethics committee in the Faculty of Pharmacy was approached to ascertain if formal ethics clearance was required for the research. As no humans or animals were involved in the study, the investigator was informed that ethics clearance would not be required and data collection commenced thereafter.

### 3.5 Initial selection of generic products

The sample size for the study was set at 20 generic products. This was done to make the pilot study more manageable. The 20 products were selected from the Generics Dictionary[16]. The 20 products were selected using a random number generator (RNG)[17] with no defined inclusion or exclusion criterion from all the products in the generics dictionary and products selected were allocated the numbers 1 – 20.

Using a hypothetical example: simvastatin is selected as one of the active ingredients chosen for the study. The number of trade names and companies that manufacture similar simvastatin preparations, in terms of dosage strength and dosage are then selected as presented alphabetically in the dictionary and, excluding the innovator product, numbered from 1 to n (n being the total). The numbers from 1 to n are entered into the RNG, the trade name allocated to number 1 is selected, and the company for that brand is included in the study. The process is represented in figure 3.2 below.

[16] Generics dictionary: a trade publication listing active pharmaceutical ingredients and the innovator and generic options available. It is used to promote the use of generic medicines. For every active ingredient, the trade names, their strengths, dosage forms, scheduling status, pack sizes, trade prices, single exit prices and other relevant prices were applicable. Volume 16 (1) Feb/March 2011 was used.

[17] An online random number generator was used: www.random.org/sequences/

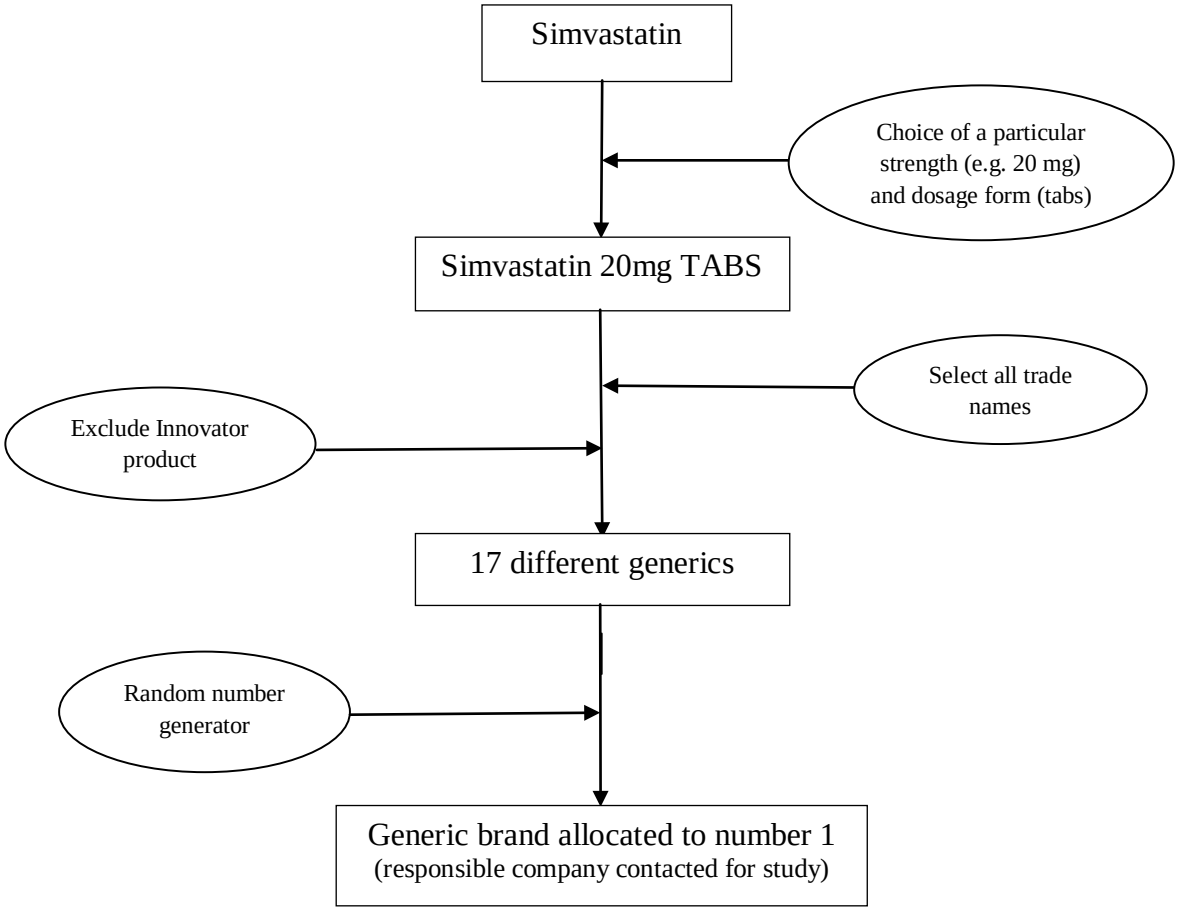


**Figure 3.2: The selection procedure of the products and companies**

The products selected represent a wide range of pharmacological classes. However, on evaluation of the initial sample, no modified release or Biopharmaceutics Classification System (BCS) class IV products[18] had been included. As a result the process was repeated to include only such products.

### 3. 6 Rationale for selection criteria

It was decided to include only modified release and BCS class IV products after discussion with experts in the field. These are the generic products about which there are concerns related to registration procedures.

#### 3.6.1 Modified release preparations

Modified release preparations are pharmaceutical preparations that do not exhibit immediate release properties.[9] According to the MCC Biostudies guideline, *in vivo* equivalence studies are required for modified release preparations designed to act by systemic absorption. *In vivo*

[18] API's that exhibit poor solubility and poor permeability

documentation of bioequivalence can either be through a pharmacokinetic bioequivalence study, a comparative pharmacodynamic study, or a comparative clinical trial.[65]

### 3.6.2 BCS Class IV preparations

BCS Class 1 APIs exhibit high solubility and high permeability. This class of APIs often qualify for waivers of *in vivo* bioavailability i.e. biowaivers, as they are characterised as rapidly dissolving.[9,64,72] Comparative dissolution studies may therefore be considered adequate to establish bioequivalence. However BCS Class IV APIs are not eligible for such waivers and require *in vivo* bioequivalence studies to establish equivalence.[65]

## 3.7 Final sample selection

The investigator identified and listed all the modified release products alphabetically by active ingredient provided more than two generics were included in the 'Generics Dictionary'. A similar list was made for the BCS Class IV products. Twenty-three modified release products were identified, and those randomly assigned the numbers 1 – 19 were selected. Two BCS class IV products were identified and the product randomly assigned the number 1 was selected.

### 3.7.1 Selection of companies

Having selected 20 modified release and BCS Class IV generic medicines, the next stage was to identify which companies were responsible for these 20 medicines. For each generic medicine, a list of trade names in alphabetical order was provided by the generics dictionary. Each trade name was associated with the name of the company responsible for it. The 20 medicines chosen were represented by nine pharmaceutical companies.

To ensure exclusion of the IPs in the selection process, the cost of the products, as listed in the dictionary were used because the IPs were significantly more costly compared to generic medicines.

## 3.8 Obtaining contact details

In communicating with the respective companies and the Registrar of the MCC, the investigator chose electronic communication using e-mail. The PAIA stipulates that requests to private bodies are to be addressed to the Chief Executive Officers (CEOs) of the respective companies. Requests to public bodies are to be addressed to the Information officer. The email addresses of the CEOs of the nine companies were obtained from various sources. A

partial list of four CEO's direct email addresses was obtained from a member of a pharmaceutical organisation. One email address was provided by an academic, but it was for the regulatory pharmacist of the company. The remaining four email addresses used were those provided by the respective companies' websites. Emails requesting the CEO's contact details were sent. Three responders requested that I forward the PAIA request and they would ensure that the request was received by the CEO. One responder provided the CEO's email address.

### 3.9 The Promotion of Access to Information Act, (Act 2 of 2000) [PAIA] and using it

The PAIA was used to formally request the information from the companies and the MCC. The Act itself was studied and analysed. The process involved in making PAIA requests was determined. 'Form A' stipulated by the Act had to be used for enquiries to public bodies; and 'Form C' to be used to request information from the pharmaceutical companies. The reason for requesting the same information from the MCC as had been requested from the companies was to attempt to validate the responses of the pharmaceutical companies.

#### 3.9.1 PAIA fees

The PAIA stipulates that both public and private bodies may charge a fee for the provision of information. The investigator requested for a waiver of the fees as the information requested was to be used strictly for academic purposes and the investigator was a full-time student with no income.

#### 3.9.2 Requests to pharmaceutical companies

The letters to the individual companies were written and the completed Form C attached to the cover letter. The cover letter gave a brief introduction of the investigator and summarised the study and the request being made. Proof that the investigator was a student was attached in the form of a registration certificate from the University and a signed letter from the supervisor. The following insert summarises the request sent to each company.

> 'Could you please inform me what tests were done to show bioequivalence for registration of the attached list of generic (interchangeable multisource) medicines, manufactured and/or distributed by your company and please state whether a domestic or foreign reference product was used?'

For the convenience of the CEO, a table was attached with columns to tick and to briefly state what tests were done. The requests were sent and the investigator waited for the responses. An example of the request to the companies is attached as Appendix 2.

### 3.9.3 Request to the MCC

The letter to the MCC was written and a completed Form A attached. As with the requests to pharmaceutical companies, proof of registration as a full time student and a copy of the supervisor's letter were attached. In addition to the Registrar being asked for the registration details of the selected 20 products, she was also asked to comment on the answer to a written parliamentary question about the use of foreign reference products over a stated period of time. An excerpt from the request is given:

> '... I am interested in the use of foreign reference products in the registration of generic medicines. I noted that the Minister of Health did not address this question when it was asked in parliament. (Question No 3021 - Internal Question Paper: 29 October 2010). The question was asked in relation to generic medicines registration 'how many were used [registered] against foreign reference products as opposed to local innovator products?'
>
> 'The answer given was that the MCC does not use generic products for comparative purposes. It appears as if there may have been a misunderstanding of what a foreign reference product is, and I would like to ask this question again, as well as to ask whether a set of twenty specific products were or weren't registered using a foreign reference product...'

A table was included to make the requested information easier to provide, and this was also attached to the request. The request was sent and the investigator awaited a response. The request is shown in Appendix 3. The full parliamentary question referred to i.e. Question 3021, is shown in Appendix 4.

# Chapter 4: Results

## 4.0 Introduction

This section presents the findings from the research. They are laid out in four parts. The first section shows the results from the enquiries made to the individual pharmaceutical companies. This is followed by a section outlining the 'responsiveness' scores (R-Scores), depicting the willingness of the pharmaceutical companies to disclose the requested information. The third section contains the responses received from the MCC and section four shows the results of the use of the Promotion of Access to Information Act (PAIA) in both private and public bodies. The enquiries made by the investigator are recorded in a smaller font and the responses received are presented in italics.

## 4.1 Data from pharmaceutical companies.

Of the requests that were sent to the nine companies, four companies provided the information. Two companies refused and three companies never replied.

**Table 4.1: Summary of nature of responses received**

| Nature of response | Number of companies |
|---|---|
| Information provided | 4 |
| Request refused | 2 |
| No response | 3 |

Figure 4.1 represents the different responses. The number of companies and number of products are shown as x(y).

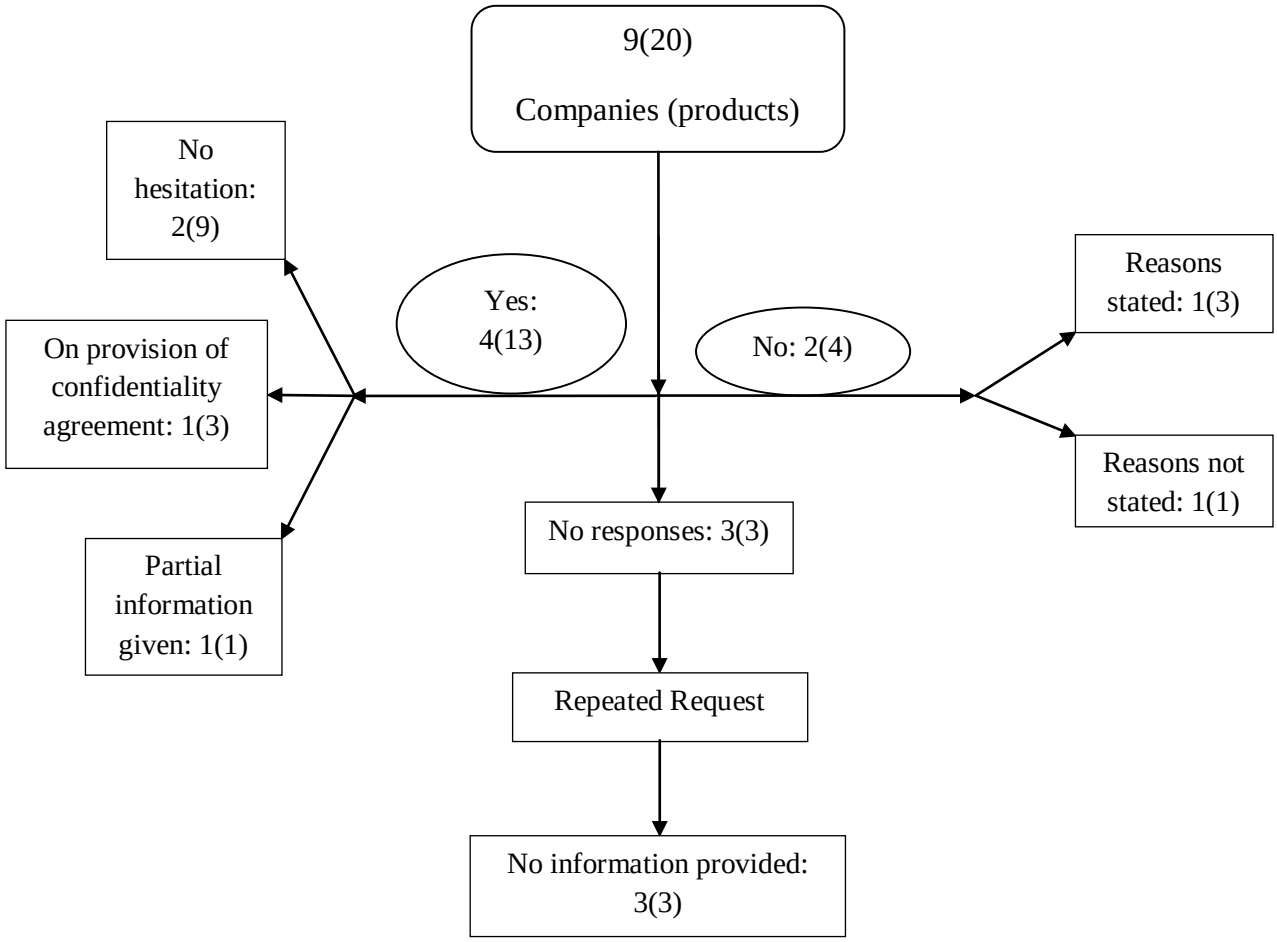


**Figure 4.1: Nature of responses; number of companies; and products for each company**

### 4.2 Communication after initial request

The interaction between the investigator and correspondents / CEOs from each company after the initial requests were made, and the first follow-up enquiries are outlined below. Section 56(1) of the Act requires private bodies to respond within 30 days of receipt of the request. Sufficient time was therefore given before any follow up correspondence was sent to the companies. (Further communications are detailed in section 4.5).

#### 4.2.1 Company A

No acknowledgement of receipt was received for the initial request of 1 June 2011, and a follow-up enquiry was made on the 22nd of July 2011:

> Dear Company A correspondent
> I would like to make an enquiry regarding the request for information using the Promotion of Access to Information Act that I made to you on the 1st of June 2011. I have to date not received an acknowledgment of receipt or a response. Kindly please advise.
> Regards

On that same day, the correspondent responded as follows:

> *'Disclosures of this nature require overseas approval, which I am awaiting... although I do not think that this will be permitted. Please follow up in a week. Thanks'*

### 4.2.2 Company B

The initial enquiry was sent on 1 June, 2011. No acknowledgement of receipt was received by the investigator and the CEO was sent an enquiry regarding the request on the 22nd of July. No response was received.

### 4.2.3 Company C

An enquiry about the request was made on the 22nd of September, 2011 as the initial request had been set on the 28th of July. The regulatory pharmacist then responded, providing the requested information for all six products. Two products had been registered using DRPs and used only *in vitro* comparative dissolution studies. The remaining four products had been tested against FRPs, three using *in vivo* bioequivalence studies and one using *in vitro* comparative dissolution studies

### 4.2.4 Company D

Following the initial request of 5th of July 2011 and no acknowledgement of receipt having been received, a follow-up enquiry was made was made on the 19th of August. No response was received.

### 4.2.5 Company E

The initial request was sent on 20 June 2011 and a follow-up enquiry was made on the 22nd of July.

On the 26th of July 2011, the following email was received from the correspondent:

> *I have received your request and unfortunately our Company will not be able to assist you with the information you require. Your understanding is appreciated.*
> *Kind regards*

### 4.2.6 Company F

The initial request was sent on 1 June 2011. The regulatory pharmacist suggested a telephone appointment to discuss the request. On the 27th of June the investigator called the regulatory pharmacist and after introductions and pleasantries, the regulatory pharmacist said:

> *'...The information you want will not be provided as it is part of the registration dossier that is submitted to the MCC...'*

She further explained that the PAIA did not apply to such information. The investigator then asked for the presentation of this response formally in writing as per the written request she had received and this was agreed to. That same afternoon, a response was received. The regulatory pharmacist indicated that the product had been registered using a FRP. To indicate acknowledgement of receipt, the response was signed and sent back.

### 4.2.7 Company G

The initial request was sent on 1 June 2011. The CEO responded on the 28th of June and indicated that the information could not be disclosed based on Section 64 (1) subsection 2 of the PAIA:

> ***Mandatory protection of commercial information of third party***
>
> ***64.*** *(1) Subject to subsection (2), the head of a private body must refuse a request for access to a record of the body if the record contains—*
> *(a) trade secrets of a third party;*
> *(b) financial, commercial, scientific or technical information, other than trade secrets, of a third party, the disclosure of which would be likely to cause harm to the commercial or financial interests of that third party; or*
>
> *(c) information supplied in confidence by a third party, the disclosure of which could reasonably be expected—*
> *(i) to put that third party at a disadvantage in contractual or other negotiations; or*
> *(ii) to prejudice that third party in commercial competition.*

He further explained that since the information being requested was not made available to the general public, and constitutes trade secrets, disclosure could cause harm to the company and its license partners. In conclusion he did say that the decision could be reconsidered if the University guaranteed that the information would not be made public. (This response resulted in the development of a confidentiality undertaking which is discussed below.)

### 4.2.8 Company H

The initial request was sent on 1 June 2011. No acknowledgement of receipt was received and a follow-up enquiry was sent on the 22nd of July. No response was received.

### 4.2.9 Company I

The initial request was sent on 1 June 2011. On 2 June an acknowledgement of receipt was received followed by a refusal of the request on the 10th of June:

> *'...After consideration of your letter, we regret to advise that we can unfortunately not provide you with the requested information based on section 64 and 65 of the Promotion of Access to Information Act 2 of 2000...'*

Section 64 and 65 of the PAIA both deal with the protection of third parties. Section 64 is quoted above (4.2.7), and Section 65 is given below:

> ***65.*** *The head of a private body must refuse a request for access to a record of the body if its disclosure would constitute an action for breach of a duty of confidence owed to a third party in terms of an agreement.*

### 4.3 Letter developed for unresponsive companies

This letter was developed as a reaction to the lack of response of some of the companies (see Appendix 5). It did not change the content or nature of the initial request in any way. The letter was sent approximately 60 days after the initial request had been sent to companies A, B, D and H, explaining the companies' legal obligation to respond to the PAIA request. According to Section 56 of the Act, a response to a request must be given within 30 days (unless a single extension of not more than another 30 days has been applied for in terms of Section 57):

> **Decision on request and notice thereof**
>
> **56.** (1) Subject to Chapter 5 of this Part, the head of the private body to whom the request is made **must, as soon as reasonably possible, but in any event within 30 days, after the request has been received** or after the particulars required in terms of section
>
> 53(2) have been received—
> (a) decide in accordance with this Act whether to grant the request; and
> (b) notify the requester of the decision and, if the requester stated, as contemplated in section 53(2)(e), that he or she wishes to be informed of the decision in any other manner, inform him or her in that manner if it is reasonably possible. (emphasis added)

### 4.4 Confidentiality undertaking

Company G had indicated that their decision could be reconsidered if the University guaranteed the information would not be made public. As a result the investigator developed a confidentiality undertaking. (Appendix 6) This guaranteed that the identities of the companies and their products would not be disclosed and that pseudonyms would be used to refer to them in all publications. Pseudonyms in the form of 'codes' were then allocated to each company. The first nine letters of the alphabet were used (A-I). Each product was then designated a number after the letter for example company B had three products; B1, B2 and B3. The list of company pseudonyms, the respective product codes and pharmacological nature of the APIs are provided in Appendix 7.

The confidentiality undertaking was co-signed by the supervisor of the project and the Dean of the Faculty of Pharmacy at Rhodes University. The confidentiality undertaking was sent to all the companies involved in the study on the 19th of August except company C to whom it was sent on the 22nd of September. For companies A, B, D and H, the confidentiality undertaking was sent along with the follow-up letter indicating that a response to a legitimate PAIA request is a legal obligation.

### 4.5 Subsequent communication with pharmaceutical companies

This section deals with the communications after the first follow-up enquiry was made. It will also cover the responses received after the companies had received the interventions in 4.3 and 4.4 above.

#### 4.5.1 Company A

As the correspondent had advised the investigator to follow-up the request after a week, a second enquiry was made on the 2nd of August.

> 'I would like to follow-up on my request for information according to PAIA dated 1 June 2011. You advised me to do so after our communication on 22 July 2011. Please advise.'

No response was received. The confidentiality undertaking and a letter highlighting Section 56 of the PAIA were sent on 19 August 2011, and still no response was received. A final enquiry was sent on the 5th of October no response has been forthcoming.

### 4.5.2 Company B

The CEO responded on the 22 August 2011, providing the requested information (after the confidentiality undertaking had been sent on 19 August). All three products had been registered using FRPs and both comparative dissolution and *in vivo* bioequivalence studies were used to prove equivalence for purposes of registration.

### 4.5.3 Company C

See above. (The initial follow-up enquiry was sent with the confidentiality undertaking attached and the regulatory pharmacist sent the requested information immediately.)

### 4.5.4 Company D

No response was received to the follow up documents. As a final follow-up, an enquiry was made on the 5th of October. No response has been received.

### 4.5.5 Company E

On the 11th of August 2011 a query was sent to Company E requesting reasons for not acceding to the initial request. No response was received. The confidentiality undertaking was subsequently sent on 19 August. A final enquiry was made on the 14th of October 2011. No response was received.

### 4.5.6 Company F

On the 12th of July 2011, the regulatory pharmacist was asked about the second part of the request i.e. tests done to prove equivalence. An excerpt from the letter is given below:

> '...I would like to acknowledge receipt of your response dated 27 June 2011. Thank you very much for the information that you have provided. Lastly, I would like to ask about the second part of my request; The test(s) done to prove equivalence. Was it dissolution testing and/or bioequivalence studies? I would be very grateful if you could furnish me with that last bit of information. If not, please may you in writing please give reasons as to why the information may not be disclosed...'

On the 13th of July, a response (Appendix 8) was received, in which it is implied that both bioequivalence studies and dissolution testing had 'been conducted'. The regulatory pharmacist explained the requirements according to the MCC for use of a FRP in the registration of a generic medicine. The pharmacist suggested that the investigator familiarise herself with the MCC guidelines.

This response was signed in acknowledgment and returned as per request. As there had been no unequivocal confirmation of the tests done to prove equivalence, a follow up email was sent to the regulatory pharmacy on the 19th of August to confirm that both bioequivalence and dissolution studies had been done to prove equivalence. The confidentiality undertaking was included with this. No response was received.

### 4.5.7 Company G

On receipt of the confidentiality undertaking, the CEO immediately responded referring the investigator to the Head of pharmaceutical development, who provided all the information requested on the 15th of September. Of the three products in question, two were registered using FRPs. Testing for both these products had involved bioequivalence studies and one had had additional comparative dissolution studies. The third product was registered using a non-FRP and comparative dissolution studies were carried out to prove equivalence.

### 4.5.8 Company H

As no response was received after having sent the confidentiality undertaking and the letter highlighting Section 56 of the PAIA, a final enquiry was made on the 5th of October. The CEO has not responded.

### 4.5.9 Company I

On the 19th of August the request was sent again along with the confidentiality undertaking in the hope that the CEO would reconsider his decision to refuse the request. On the 23rd of September the CEO replied, refusing the request a second time, (see Appendix 9). The CEO indicated that he was of the view that the PAIA request was not consistent with the intention of the Act neither did it conform to the Act as they did not consider the right to academic and scholarly endeavour ‘a recognised right in terms of the Constitution’.

Table 4.2 shows the dates when the initial requests were sent, when key responses and the final responses were received and when the confidentiality agreement (CU) was sent.

**Table 4.2: Dates of communication with companies**

| Pseudonym | Products | Date 1st request was sent | Date CU was sent | Date of final response |
|---|---|---|---|---|
| **A** | A1 | 01/06/2011 | 19/08/2011 | X |
| **B** | B1-B2 | 01/06/2011 | 19/08/2011 | 22/08/2011 |
| **C** | C1-C6 | 28/07/2011 | 22/08/2011 | 22/08/2011 |
| **D** | D1 | 05/07/2011 | 19/08/2011 | X |
| **E** | E1 | 20/06/2011 | 19/08/2011 | X |
| **F** | F1 | 01/06/2011 | 19/08/2011 | 13/07/2011 |
| **G** | G1-G3 | 01/06/2011 | 19/08/2011 | 28/09/2011 |
| **H** | H1 | 01/06/2011 | 19/08/2011 | X |
| **I** | I1-I3 | 01/06/2011 | 19/08/2011 | 23/09/2011 |

**CU = Confidentiality Undertaking; X = No final response provided**

Table 4.3 summarises and shows the responses from each company regarding each product. Responses were received for 13 of the 20 products in question. Ten of the 13 products were registered using FRPs.

**Table 4.3: Results from responsive companies**

| Company | Product | Nature of product | FRP Used? | Tests done | Higher dose Registered? |
|---|---|---|---|---|---|
| **B** | B1 | Anti-cholesterol | Yes | Bioequivalence and comparative dissolution | No |
| | B2 | Vasodilator | Yes | Bioequivalence and comparative dissolution | No |
| | B3 | Anti-depressant | Yes | Bioequivalence and comparative dissolution | No |
| **C** | C1 | Anti-epileptic | No | Comparative dissolution | Yes |
| | C2 | Anti-hypertensive | No | Comparative dissolution | No |
| | C3 | Anti-hypertensive | Yes | Bioequivalence | No |
| | C4 | Mineral supplement | Yes | Comparative dissolution | No |
| | C5 | Analgesic | Yes | Bioequivalence | No |
| | C6 | Anti-arrhythmic | Yes | Bioequivalence | No |
| **F** | F1 | Anti-inflammatory | Yes | Bioequivalence and comparative dissolution | No |
| **G** | G1 | Anti-arrhythmic | Yes | Bioequivalence and comparative dissolution | No |
| | G2 | Anti-inflammatory | No | Comparative Dissolution | Yes |
| | G3 | Anti-epileptic | Yes | Bioequivalence | No |

### 4.6 The 'level of responsiveness' of the pharmaceutical companies

This is depicted as an 'R-Score'. It is based on the information that was provided by the companies. The score represents the willingness of the companies to voluntarily[19] provide the requested information. The highest possible score was achieved when the company provided all the requested information and the lowest score was received when the company failed to respond to the request at all. Tables 4.4 and 4.4A below show the R-score and interpretations for the nine companies involved in the study.

**Table 4.4: R-Score for pharmaceutical companies**

| **RRRR**<br>**Information provided with no hesitation** | **RRR**<br>**Information provided after confidentiality undertaking** | **RR**<br>**Some of the requested information provided** |
|---|---|---|
| B | G | F |
| C | | |
| **R**<br>**Requested declined, reasons given** | **RX**<br>**Request declined, reasons not given** | **X**<br>**Request ignored** |
| I | E | A |
| | | D |
| | | H |

**Table 4.4A: R-Score for pharmaceutical companies A - I**

| **Company** | **R Score** |
|---|---|
| **A** | **X** |
| **B** | **RRRR** |
| **C** | **RRRR** |
| **D** | **X** |
| **E** | **RX** |
| **F** | **RR** |
| **G** | **RRR** |
| **H** | **X** |
| **I** | **R** |

[19] As there were errors in the wording of the PAIA requests, the responses received can be considered voluntary disclosures.

### 4.7 Request to the MCC for information

The PAIA request was dated 24 May 2011. The Registrar of Medicines replied and referred the investigator to a Mr GJ Wissing, the Deputy Information Officer (DIO) of Legal Services of the Department of Health. The request was immediately forwarded to him. A follow-up enquiry was made on the 20th of June as no acknowledgement of receipt had been received from him. A response was received on the 20th of July when the request was refused in terms of Section 45 (b) of the PAIA (Appendix 10).

> *(b) the work involved in processing the request would substantially and unreasonably divert the resources of the public body.*

The DIO also cited Section 36 of the PAIA: *Mandatory protection of commercial information of third party* and recommended that the information be obtained directly from the pharmaceutical companies.

#### 4.7.1 Evaluation of the Initial response

The MCC refusal was analysed and the investigator decided to lodge an internal appeal.

### 4.8 Internal appeal

The Internal appeal was lodged in terms of Section 74 of the PAIA. It consisted of a cover letter, a completed compulsory Form B, and a document titled 'the grounds of appeal'. The grounds of appeal are a justification as to why the information should be disclosed to the investigator (see Appendix 11). An excerpt from the grounds of appeal is given:

1. '...It is not unreasonable to anticipate that the Regulatory Authority should be able to access the product files of any product at any given time.
2. Section 15(7) of the Medicines and Related Substances Act (Act 101 of 1965) states that:

   **Any registration under this section, including the registration of medicines already registered . . . may be made subject to such conditions as may with regard to the succeeding provisions of this section be determined by the council.**

As every medicine is registered with 'conditions of registration' it must mean that should any query about the basis for a particular condition of registration be raised, the MCC can at any time access the product files (dossier) of a medicine's application. Accessing the product files would therefore surely be a normal part of the regulatory authority's everyday activities and Section 45(b) of the PAIA (Act 2 of 2000) would not apply...'

The appeal was sent to the Registrar and the investigator was referred again to the DIO. A response was awaited. On the 11th of October a follow-up enquiry was sent to the DIO.

### 4.9 Final MCC response

A second refusal of the request was received from the DIO on the 21st of October. (Appendix 12). The decision to dismiss the appeal was stated to have been made by the relevant authority (the Minister of Health), and Sections 36 and 45 of the PAIA were given as grounds for the MCC's refusal. These are:

> ***Mandatory protection of commercial information of third party***
>
> ***36.*** *(1) Subject to subsection (2), the information officer of a public body must refuse a request for access to a record of the body if the record contains—*
> *(a) trade secrets of a third party;*
> *(b) financial, commercial, scientific or technical information, other than trade secrets, of a third party, the disclosure of which would be likely to cause harm to the commercial or financial interests of that third party; or*
> *(c) information supplied in confidence by a third party the disclosure of which could reasonably be expected—*
> *(i) to put that third party at a disadvantage in contractual or other negotiations; or*
> *(ii) to prejudice that third party in commercial competition.*
> *(2) A record may not be refused in terms of subsection (1) insofar as it consists of information—*
> *(a) already publicly available;*
> *(b) about a third party who has consented in terms of section 48 or otherwise in writing to its disclosure to the requester concerned; or*
> *(c) about the results of any product or environmental testing or other investigation supplied by, carried out by or on behalf of a third party and its disclosure would reveal a serious public safety or environmental risk.*
> *(3) For the purposes of subsection (2)(c), the results of any product or environmental testing or other investigation do not include the results of preliminary testing or other investigation conducted for the purpose of developing methods of testing or other investigation.*
>
> ***Manifestly frivolous or vexatious requests, or substantial and unreasonable diversion of resources***
>
> ***45.*** *The information officer of a public body may refuse a request for access to a record of the body if—*
> *(a) the request is manifestly frivolous or vexatious; or*
> *(b) the work involved in processing the request would substantially and unreasonably divert the resources of the public body.*

The DIO further stated that the motivation for the appeal had failed to indicate how the disclosure of these records would give evidence of contravention of a law and/or a serious public risk.

The DIO did not however respond to that part of the request regarding the MCC PAIA manual. On the 26th of October 2011, the DIO was sent another letter, acknowledging receipt

of the reply and again requesting a copy of the MCC's PAIA manual (Appendix 13). As a final follow up, an enquiry was made on the 15th of November. No response was received and it was concluded that the MCC does in fact not have a PAIA manual.

# Chapter 5: Discussion

## 5.0 Introduction

This chapter analyses and discusses the results from chapter four and the objectives set for the research (page 4).

The use of an action research methodology within a case study framework proved to be a most appropriate approach to conducting this study. The information obtained from the pharmaceutical companies, followed by the R-Score[20] analysis, the results from the Medicines Control Council (MCC), issues related to the MCC guidelines, the MCC's regulatory role, the interchangeability of medicines, the tender system, concerns about foreign reference products (FRPs) and dissolution testing, intellectual property rights, legal liability and finally the application of the Promotion of Access to Information Act, Act 2 of 2000 (PAIA) in the context of this study are all discussed. This includes the use of the PAIA from a 'layperson's' perspective and some of the errors made.

The data from chapter four, and the literature from chapter two are included. Unless otherwise stated the MCC guidelines referred to in this chapter are the June 2011 Pharmaceutical and Analytical (P&A) and Biostudies guidelines; and the March 2011 Dissolution guideline.

The case study framework with a deliberately small sample size means that the results cannot in any way be generalised. No definitive conclusions about the use in South Africa of foreign reference products or the tests used to demonstrate therapeutic equivalence in the registration of generic medicines, can be made. However, it may provide some background information for further research.

## 5.1 Responses from pharmaceutical companies

The decision to inquire about modified release and BCS IV preparations was a deliberate one in that the MCC guidelines do not recommend dissolution tests 'on their own' for registration of these products. As all modified release products have to show evidence of the mechanism of modified release of the reference product, this information was not requested in this study.

[20] R-Score: A 'responsiveness score' developed to depict the willingness of the pharmaceutical companies to voluntarily respond to PAIA questions.

According to the MCC's Pharmaceutical and Analytical guideline, modified release dosage forms include 'delayed-release dosage forms', and 'extended-release dosage forms'. It is noted in the guideline that the terms 'controlled release', 'prolonged action' and 'sustained release' are used synonymously with 'extended release'.[9]

For five of the thirteen products about which information was provided, both *in vivo* and *in vitro* methods were used. As is the norm and part of the rationale for the very existence of generic medicines, none of the products had undergone clinical trials. Of the thirteen products, ten used a FRP as a comparator for registration. The sources (origins) of the different FRPs used as comparators for those products were not requested or identified. If none of the seven products for which no information was made available were registered using a FRP, this would mean that 50% of the small sample chosen were registered against a FRP. This seems at face value to be significant (in the sense of important rather than statistically significant).

*In vitro* comparative dissolution studies were used as a standalone means of approval for four of the thirteen products, (three with DRPs and one with a FRP as comparator). It is possible that the one product registered using a FRP as comparator and only *in vitro* dissolution studies could have been given a biowaiver upon motivation by the applicant, but no evidence of this is available. In future research it would be worth asking whether or not a waiver had been granted if comparative dissolution studies have been used as a standalone means of approval. The use of FRPs for purposes of registering generic medicines seems to be a reality in the pharmaceutical industry in South Africa. It would be interesting if further research could be done to determine the percentage of generic medicines that have been registered using FRPs as comparators. It would also be useful to determine the attitudes of prescribers and dispensers towards the use of FRPs for registration purposes and whether or not they believe this is information that should be made available to them and why.

### 5.1.2 Modified release products – biowaivers

Biowaivers for *in vivo* equivalence studies may be granted when a higher dose of the same product has already been registered. Dissolution testing and comparison of dissolution profiles may in certain instances then be used alone for lower doses.[65]

For the three products where the DRP was used i.e. products C1, C2 and G2, only comparative dissolution studies were used for registration. Biowaivers may be granted for modified release preparations when the proposed product is proportionally similar to a

product that has already been approved and is on the market. Conditions come with this exemption. These conditions include that the lower strengths of the product are in the same dosage form as the higher strength, that they exhibit the same release properties and are proportionally similar in their active and inactive ingredients. The products must also be manufactured by the same manufacturer and at the same site as the registered generic.[65,67] Higher strengths of the medicines are available for C1 and for G2. It is therefore reasonable to assume that these higher strengths were appropriately tested before approval and C1 and G2 were eligible for bio-waivers and comparative dissolution testing was sufficient for registration. The manufacturers were however not specifically asked about the testing of the higher strengths and this is a limitation of this study. C2 however does not have a higher strength and would seemingly not have qualified for a bio-waiver.

Products C1-C6 and G3 all had only one of the required tests done. The four products from Company C that were registered using only *in vivo* bioequivalence studies were all registered against FRPs. It should be a concern that dissolution tests were not carried out as well. As G3 is an anti-epileptic drug registered against a FRP and no higher strength is available, it is of possible greater concern given the serious nature of epilepsy and the possibilities of break-through seizures with a modified release product occurring.

### 5.1.3 Product C4

Product C4 is of particular interest. It was the only product registered against a FRP where only comparative dissolution testing and no bioequivalence studies were done. C4 does not qualify for a bio-waiver as it is made in a single strength only. No enquiry was made to the company as to why bioequivalence studies were not done on this product. It seems unlikely that the members of the relevant committee of the MCC would have overlooked this, but it is possible that the pharmaceutical industry itself does not always adhere to the regulatory authority's guidelines, and the product 'slipped through the cracks'. However C4 is a mineral supplement. In general mineral supplements are not required to undergo bio-availability studies. Whether mineral supplements with modified release properties are required to undergo bio-equivalence studies for purposes of registration is not clear and the MCC guidelines do not make specifications for modified release mineral supplements. It could be argued that a bioequivalence study was not necessary. On the other hand an overdose of this particular mineral supplement could have life threatening consequences, so perhaps a blanket approach to modified release mineral supplements being registered based on comparative

dissolution testing alone is not appropriate. No enquires were made to the MCC and manufacturer of C4 to explain why it was seemingly exempted from bioequivalence studies

### 5.1.4 BCS Class IV product

As the company to which the request for information regarding the BCS class IV product was sent did not respond, it is not known whether or not it was registered against a FRP or what tests were used. It may have been a better decision for this study to use both BCS class IV generic medicines listed in the Generics Dictionary rather than just one of them. BCS class IV products, which are problematic in terms of permeability and solubility, require *in-vivo* bioequivalence studies.

## 5.2 The confidentiality undertaking

The confidentiality undertaking became a loop in the action research process. The wording of the initial request was not changed, however anonymity was introduced into the research as a result of one of the companies stating that they would provide information on condition that a confidentiality agreement was incorporated. Action research techniques allow one to evaluate and introduce additional aspects into the study, modify it where necessary and continue. This proved to be an advantage of using this methodology for this study.[114]

### 5.2.1 Responsiveness of the pharmaceutical companies

The 'R-Score' was initially conceptualised based on the *Australian Prescriber* Journal's transparency score (T-score). [110,111] As the PAIA requests made to the companies erroneously asked for specific information within records instead of specifying the records which the researcher wished to access, the companies were under no obligation to provide the information in terms of the PAIA. That they did so voluntarily may indicate that they too did not fully comprehend the parameters and requirements of the PAIA.

The 'R-Score' therefore simply represents the responses received voluntarily from the pharmaceutical companies. Differences within categories were catered for. For example, though companies B, C, F and G all provided information, it was under different circumstances and the nature of the information was different. This led to companies being assigned different 'R-Scores'. Companies B and C received the highest score of '**RRRR'** and can be stated to have been the most responsive of the nine companies as the full information was provided and no hesitation or reservations were shown. The time taken to furnish responses to the requests was not incorporated into the scores as it was acknowledged that

CEOs have very busy schedules (and the PAIA makes it the CEO's responsibility to respond, although it does stipulate a time line of 30 days with the option of a request for a single extension of another 30 days). Company G agreed to provide the information only on condition of guaranteed anonymity and hence received the second highest score of **'RRR'**.

The **'RR'** score indicated that company F had provided the information but hesitation was clear, and there was some vagueness in the response. Not surprisingly the regulatory pharmacist for company F demonstrated an awareness and knowledge of the MCC requirements for registration. After stating these, she wrote:

> *'As such, if a foreign reference product was used in the registration of a generic medicine, it follows that both a bioequivalence and dissolution study has been conducted.'* (emphasis added)

It would seem the intention was that the researcher should assume that it was obvious that the appropriate studies had been done for the product in question, F1. (Appendix 8) The regulatory pharmacist's response could be perceived as not wanting to be specific and make a definitive statement – for whatever reason. Efforts to clarify and verify the information received no response.

In the cases where the companies refused the requests outright, the only differentiation made to the 'R-score' was whether or not a reason was given for the refusal. In terms of the PAIA, a reason had to be provided as to why the request was denied. Companies I and G were clearly aware of this and quoted Sections 64 and 65 of the PAIA as reasons for refusal. Company E however failed to give any reasons.

The allocation of an 'R-score' of **'X'** was for companies who did not provide the requested information had no divisions as all companies were unresponsive. Although company A acknowledged receipt of the request as compared to companies D and H, no information was actually then provided. It is a possibility that the requests for information were not taken as seriously because a student was making them. It is also possible that these three companies identified that the PAIA had been used incorrectly, and that they had no legal obligation to respond. For companies D and H, it could be argued that the email addresses used were not viable or were wrong, however this is unlikely. The email address for the CEO of company D was provided by the correspondent from the company and no notification of 'failure of delivery' or 'out of office' was received for either company.

Companies G and I indicated in their refusals that they were protecting unnamed third parties. This response is specified in the PAIA itself. The companies may have felt that this particular

information, if it became public knowledge might reduce sales or harm the company image. Prescribers and/or dispensers of their medicines might become suspicious of products evaluated against foreign comparators. This could in turn have adverse consequences for the companies. The irony is that FRPs may well be quite acceptable in terms of quality, safety and efficacy – but in South Africa this is largely unknown and further research should be done to verify this.

### 5.2.2 Intellectual property

Protection of intellectual property rights (IPR) could be one of the reasons why companies would not wish to disclose information. However, no specific details about the names and sources of reference products were requested. The request also did not enquire about manufacturing processes or formulations which can be said to be 'owned' by the companies. These are the kinds of details that would generally be viewed as sensitive and considered as intellectual property.[116] Furthermore bioequivalence and dissolution tests are not novel tests that can be said to 'belong' to a company. They are used across the world in the pharmaceutical industry and the MCC guidelines describe how these tests are to be performed for the registration of medicines in South Africa. Which tests were done in registering a product would not be considered intellectual property since the tests required to prove equivalence are public information.[65,67] It is possible that the companies were importing their products and this was what was meant by the 'third parties'. Some of the companies have 'parent companies' overseas, which is implied in Company A's response. It is possible that the 'third parties' referred to are these parent companies.

## 5.3 Response from the MCC

The first thing to be noted from the MCC's response to the initial request was that the MCC has no up to date electronic database containing the information about all registered medicines. Dossiers are very large collections of documents and creating the electronic storage of all the details in them would be a gargantuan task for all the registered products already on the South African market. That being said, the fact that the MCC is unable to easily and rapidly access details regarding medicines that have been registered is cause for concern. Their failure to provide the mandatory PAIA manual is also cause for concern. As much as this is so, it is acknowledged that the request made to the MCC was inappropriately phrased. The request (Annexure 3) was for the 'contents of records' and not 'specified records' as required by the PAIA. The MCC therefore was not obliged to provide the information to the investigator and correctly refused to do so.

### 5.3.1 The response to the parliamentary question

A component of the request to the MCC was the inclusion of the Minister of Health's response to a written parliamentary question. Responses to parliamentary questions can be particularly useful as they are required to be truthful, although there are anecdotes about how certain questions are avoided or minimised. Answers to parliamentary questions are also in the public domain. Parliamentary questions can be used to obtain information, or at times may have a more devious objective such as embarrassing government. As the parliamentary question had been put to the Minister of Health by a member of the opposition party, one can assume that it was treated with caution by government. The response given was in this researcher's view inadequate. The intention of the question (as understood by the researcher) was that it would give details of the extent (perhaps as a percentage) of the use of foreign reference products in the registration of generic medicines. The Minister's response which was that the MCC does not use generic medicines as comparators indicates a possible deliberate avoidance of directly providing the information requested. The Registrar however was of the view that the question, as asked, had been answered appropriately and stated that the question had not asked about the extent to which FRPs are used as comparators in registering generic medicines. Technically the Registrar's view is incorrect because if no innovator product is on the market a 'generic' may well be used as a comparator for registration of another generic medicine. The response could be interpreted as being an indication that the answer is unknown. However a rough estimate in words could well have been provided such as 'most' or 'minimal' generics are registered using FRPs as comparators.

The use of FRPs as comparators appears to be widespread however, and their use in the small sample in this study seems to bear this out.

### 5.3.2 The internal appeal and second refusal

On refusal of a PAIA request from a public body, an internal appeal can be made in terms of Section 74(1) of the Act. An internal appeal is submitted by the requester calling for the decision regarding the request to be reconsidered. The appeal is accompanied by the grounds of the appeal to justify why the information is to be furnished. In their response to the appeal, the letter signed by the DIO of the Department of Health again made reference to both Sections 36 and 45 as in the initial refusal. Particular emphasis was placed on Section 45(b) and it was stated that the Minister of Health, as the higher authority to whom the internal

appeal had been referred was 'of the opinion that it would be completely unreasonable for the MCC to have to go through each and every dossier to answer (1) in your original request.'

In the PAIA CSN shadow report a lack of resources is noted as a reason why the implementation of PAIA is a challenge. Poor records management is also stated as a factor affecting implementation.[100] The response to the internal appeal quoting Section 45(b)[21] is of a similar nature to the findings in the shadow report.

**5.4 Changes in the MCC guidelines.**

In considering the MCC's regulatory role, guidelines are not considered to be strict rules or the law. They are seen as a guide to show how things ought to be done. The guidelines begin with a statement that they are 'recommendations' for completing applications for registration of medicines. The guidelines make it clear that they are not to be considered an exclusive approach and that additional information may be required. Alternative approaches may furthermore be suggested with sufficient justification. Guidelines for industry are also provided by the WHO, and in other countries e.g. USA and Europe.[120-122]

The MCC guidelines have changed over the years, including those applying to the use of FRPs and the tests required for the proof of equivalence. The guidelines seem to reflect an increasing flexibility on the part of the regulatory authority since the initial introduction of generic medicines. From an initially fairly rigid process where the only recognised reference product was the innovator product, there are now four options for choice of a reference product in the most recent Pharmaceutical and Analytical guideline. With dissolution testing being accepted as a means of proving equivalence for certain predefined products, a cheaper and faster means was provided to the industry. Furthermore, the use of dissolution studies has become widespread and is used even in cases where it may not be the most appropriate test. Circular 14/89 of 1989 only gives indications of when dissolution studies may be used. They do not specify instances in which they are <u>not</u> appropriate. For example, dissolution testing would presumably be entirely inappropriate for topical medicines.

It is not clear to what extent dissolution studies are being used on their own for the registration of generic modified release preparations – despite the fact that the guidelines state that *in vivo* bioequivalence studies must be carried out for these products' registrations. It is argued that it would be unreasonable to require every generic medicine to undergo full clinical trials. This would be time consuming, expensive and unethical.[58] However <u>not</u>

[21] 'the work involved in processing the request would substantially and unreasonably divert the resources of the public body'

performing the clinical trials must not result in any compromise of quality, safety and efficacy of the medicines. Requirements for both *in vitro* dissolution studies and *in vivo* bioequivalence studies must be clearly stated without any ambiguity or room for misinterpretation. The NAPM[22] itself has stated:

> 'Generic medicines are subject to the same scrutiny by regulatory authorities as products of original research. Stringent requirements of South Africa's Medicines Control Council ensure that the quality and efficacy of generic medicines mirror that of the original product...'.[45] (emphases added)

The MCC's June 2007 Pharmaceutical and Analytical guideline made the following cautionary statement:

> 'A product that has been approved based on comparison with a non-domestic reference may or may not be interchangeable with currently marketed domestic products.'[77]

The June 2011 Pharmaceutical and Analytical guideline does not contain the same warning. It is fair to assume that in placing this caution in the 2007 guideline the regulatory authority is aware that interchangeability between products registered using FRPs and the DRP may not be ideal or is even potentially problematic. This statement is in line with what Kanfer states:

> 'In the absence of specific confirmatory data i.e. comparative bioavailability data, a non-domestic [foreign] comparator product used as a the reference product in a bioequivalence study involving a generic product intended for a particular domestic market cannot be assumed [or considered] to be bioequivalent to the domestic innovator product.'[22]

Perhaps prescribers, dispensers and possibly even patients should be aware of medicines where no comparative bioavailability data have been submitted by the applicant or evaluated by the MCC, so that an informed decision can be made about generic substitution by these stakeholders. This is particularly relevant in the South African context where dispensers of medicines are required by law to substitute generic products unless the prescriber has prohibited it or the patient refuses it.

The prescribers, dispensers and patients would usually have no interest in checking industry guidelines to obtain information even though they are publicly available on the MCC's website. They are most likely unaware of the guidelines and no information is provided to these stakeholders about the use of FRPs or the tests used in registering products. The system is thus geared towards 'blind trust' in the regulatory authority.

Consideration should be given to amending the Regulations to the Medicines Act to include providing prescribers and dispensers with the origin of the comparator reference product and

[22] NAPM: National Association of Pharmaceutical Companies.

the tests used to prove equivalence. This could possibly be included in the medicines' package inserts. Similar information in simplified yet accurate language could be included in the mandatory patient information leaflets if deemed desirable[23]. Consideration would have to be given as to whether or not such information would also need to be included on the labels and outer packaging of the products. The WHO encourages regulatory authorities to communicate with their clients regularly, acknowledging the right of citizens to receive accurate and appropriate information from the authority, and especially about medicines marketed in their country.[1]

The question as to why the cautionary note was excluded from the updated version of the Pharmaceutical and Analytical guideline must be asked. Was it a result of pharmaceutical industry pressure on the secretariat of the MCC? Was it pointed out to the Council members of the MCC that it had been removed when they approved the new guideline? Does the MCC now believe that products approved based on comparison with a non-domestic reference are 'always' interchangeable with currently marketed domestic products?

### 5.5 The Role of the MCC

The MCC has the statutory responsibility to ensure that all available medicines have satisfied the requirements for quality, safety and efficacy.[61,62] While this study may suggest over-flexibility in generic medicines' registration, Tobin concludes that the MCC 'over-regulates' the pharmaceutical industry in its pharmaceutical policies.[123] Her study compared the MCC's requirements with the requirements and guidelines of the USA and EU medicines regulatory authorities.[24]

Tobin's conclusions were that the MCC seemed to take a more academic approach when it comes to medicines registration, while the industry took a more practical (pragmatic) stance. Some of the 'additional' requirements of the MCC (compared to the overseas authorities) were viewed to be unnecessary, not adding extra value to the product and often impractical by the industries.[123] As a regulatory authority, the MCC is required to exercise its authority in terms of the legislation (and the parliamentary mandate) for the protection of the people of South Africa. The MCC can even be commended for taking a more rigorous stance as it seems to highlight a more patient-focused, rather than industry-focused approach with regards to medicines' registration. (It would seem however that the increasing flexibility that

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[23] Issues of adherence (compliance) would need to be carefully considered amongst others.

[24] The Food and Drugs Administration (FDA) and European Medicines Agency (EMA) respectively

has been developing over the years may be shifting more towards an industry-friendly approach.) It should be noted that the MCC relies heavily on academics to work in its committees and as members of the Council itself. The FDA and EMA rely more heavily on full time employees. The latest amendment of the Medicines Act (Act 72 of 2008) which has been assented to by the President but not yet promulgated[25], will abolish the MCC and replace it with a structure closer to that of the FDA.

The 2011 High Court case concerning the MCC's resolution that dextropropoxyphene (DPP) be withdrawn was won by the MCC against Adcock Ingram. This is an indicator of the vital role that the MCC plays in the protection of the people of South Africa, and that in some areas the MCC is fulfilling its mandate.[124,125]

### 5.6 Interchangeability

Another potential problem area needing to be addressed is that of the meaning of interchangeability. It is defined in the Medicines Act (Section 1) as follows:

> **'interchangeable multi-source medicine'** means medicines that contain the same active substances which are identical in strength or concentration, dosage form and route of administration and meet the same or comparable standards, which comply with the requirements for therapeutic equivalence as prescribed

The prescribed requirements for therapeutic equivalence are defined in Regulation 2 of the Regulations to the Medicines Act as follows:

> A medicine is considered therapeutically equivalent to another medicine if both medicines-
>
> (a) are pharmaceutically equivalent, i.e., contain the same amount of active substances in the same dosage form, meet the same or comparable standards and are intended to be administered by the same route; and
> (b) after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same.
>
> Therapeutic equivalence is determined from comparative bioavailability, pharmacodynamic, clinical or *in vitro* studies which meet the requirements and accepted criteria for bioequivalence as determined by the Council.

The Regulations to the Act define bioequivalence as follows:

[25] In March 2012 this version of the Medicines Act was returned to parliament as the 'Medicines and Related Substances Amendment Bill 2012'.

> **'bioequivalence'** means the absence of a significant difference in the bioavailability between two pharmaceutically equivalent products under similar conditions in an appropriately designed study'

Bioavailability is not defined in the Act or Regulations but in the MCC's 'Biostudies Guideline' Version 5, June 2011 it is defined as:

> 'Bioavailability refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. It may be useful to distinguish between the 'absolute bioavailability' of a given dosage form as compared with that (100 %) following intravenous administration (e.g. oral solution *vs.* intravenous), and the 'relative bioavailability' as compared with another form administered by the same or another non-intravenous route (e.g. tablets vs. oral solution).'

These three definitions are shown in Table 5.1

**Table 5.1 The elements of the definitions for generic medicines**

| Interchangeable multi-source medicine (generic medicine) | Therapeutic equivalence | Bioequivalence |
|---|---|---|
| | Pharmaceutically equivalent | Pharmaceutically equivalent |
| same active substances | Same amount active substances | [Same amount active substances; same dosage form; same route of administration; same or comparable standards] |
| Identical in strength (concentration) | | |
| Identical dosage form | Same dosage form | |
| Identical route of administration | Same route of administration | |
| Meet same or comparable standards | Same or comparable standards | |
| Prescribed requirements for therapeutic equivalence | | |
| | After administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same. | [After administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same.] |
| | Determined from comparative bioavailability, pharmacodynamic, clinical or *in vitro* studies which meet the requirements and accepted criteria for bioequivalence | **[**Determined from comparative bioavailability, pharmacodynamic, clinical or *in vitro* studies which meet the requirements and accepted criteria for bioequivalence] |
| | | No significant difference in bioavailability under similar conditions in appropriately designed study. |

Put simply, a generic medicine must be i) therapeutically equivalent, ii) pharmaceutically equivalent and iii) bioequivalent.

The question must be asked whether or not dissolution testing and bioequivalence studies can be relied on to show that 'after administration in the same molar dose, their effects with respect to both **efficacy and safety** are essentially the same'. It could be argued that efficacy and safety could in fact only be shown with clinical studies.

### 5.6.1 The Tender System in South Africa

The purpose of the tender system is to allow government, which supplies medicines at no charge to the majority of the population, to attempt to do so in a more cost effective manner. According to the National Drug Policy of SA (1996), the use of generic medicines shall be prioritised; this is mandated in the MARS[26], Section 22F to reduce the cost of medicines. Contracts for tenders may range from six months to one year or more. This means that patients who depend on the public sector for their medicines may not receive medicines that look the same every month, even if they contain the same concentrations of the active ingredients. This lack of consistency particularly affects patients on chronic medicines. If a supplier defaults (or is unable to fully supply medicines for the duration of the tender) and replacements are obtained from another manufacturer, it means the patients will be receiving a different generic product. It is possible that this generic product was registered against a FRP and has not been proven bioequivalent or therapeutically equivalent to the innovator product or even the previous generic product. Changes in the appearance of medicines often confuse elderly patients and there is an unwillingness of some patients to move to a different brand of their regular medicines. This could result in a lack of adherence as often colour and appearance assist in identifying which medicines to take and when to take them.[50,126,127]

This problem does not only affect the public sector. Generic medicines available to patients in the private sector also change. The private sector is driven by medical schemes and is also impacted when the lists of brands which are permitted and covered by the scheme are changed.[35] Besides medical aid schemes, community pharmacists may change their stock of generic medicines depending on prices. The 'big chain' pharmacies are probably more able to stock a wider variety of the same generic medicines, and hence access may be more consistent for a patient. However a community pharmacist should always be able to order a generic which is preferred by a patient or prescriber.

[26] Medicines and Related Substances Act as amended (Act 101 of 1965)

The problem with switching between two generic products is that they are not necessarily interchangeable.[60] The use of different excipients, manufacturing processes and manufacturing equipment often results in changes in bioavailability.[22] Besides that, when looking at the bioavailability limits in South Africa, they range from 80% to 125% for AUC and range from 75% to133% for Cmax at a 90% confidence interval.[22,63] This potentially means that for the AUC significant differences in the API bioavailability could be permitted between two generic pharmaceutical products. A potential bioavailability difference of up to 45% is possible.[22] While one generic product may have been registered after proving that it is has 120% bioavailability, another may have been registered which has 85% bioavailability.

The need for a narrower reference range (perhaps at a 95% confidence interval) should possibly be considered for comparators in the registration of generic medicines. Where an innovator product (IP) is manufactured locally, perhaps this should be considered the most desirable reference standard and not FRPs.

### 5.7 Concerns using FRPs

The use of FRPs in establishing equivalence presents certain challenges that may be overlooked in the guidelines. Permitting the use of FRPs requires that the MCC closely monitor the sources of the FRPs used. Perhaps it would become necessary for the MCC to require that only one source of an FRP is used for each active pharmaceutical ingredient in generic medicines in an effort to create uniformity. Unfortunately, it was not possible in this study to determine what the sources of the different FRPs used were. This can be considered a limitation in this study.

### 5.8 Concerns regarding dissolution testing

Dissolution testing is commonly used as a 'surrogate' test for *in vivo* bioequivalence studies. It is not however always accurate in determining and predicting bioavailability and bioequivalence.[18,62] If dissolution testing alone were capable of establishing equivalence; there would be no need for *in vivo* bioequivalence tests. While the use of dissolution studies as a surrogate significantly reduces the time and cost involved in proving equivalence, it was developed initially as a quality assurance tool and to assist in the selection of chemical candidates for research.[18] It is not a prognostic tool for drug absorption.[66]

Studies to establish *in vitro-in vivo* correlations through dissolution testing for modified release preparations are continuing.[128-130] This would mean that after doing *in vitro* dissolution studies, the therapeutic effects of the same product *in vivo* could be predicted.

This has not yet been established for modified release systems as they are present in the gastro-intestinal tract for a longer time and both fed and fasting conditions need to be considered.[129] Until sufficiently accurate guidelines can be determined for the use of *in vitro-in vivo* correlations for modified release preparations, *in vitro* dissolution testing cannot be used alone in determining therapeutic equivalence. Having determined the therapeutic equivalence of a particular dose of a modified release product however, it may then be permissible to use dissolution testing for other strengths of the same product.[65]

### 5.9 Legal liability

Pharmacists are the 'custodians' of medicines. They are responsible for their safe keeping as indicated in both the MARS and Pharmacy Acts. Given Section 22F of the MARS which obligates pharmacists to dispense generic medicines, the question arises as to whether a pharmacist could be held legally liable for dispensing such a generic medicine in the event that (serious) adverse drug reactions occur.[58] A liability suit could theoretically be based on the expectation that, even if a generic medicine had been registered by the MCC, the pharmacist had failed to ensure that the generic product that was substituted was indeed therapeutically equivalent to the prescribed or domestic innovator product. This requires that pharmacists unequivocally trust the MCC's registration processes. If the package insert of a medicine were to provide details of the source of a generic medicine and/or the basis on which it was registered (e.g. the details of a FRP if used, and what other testing was used) perhaps pharmacists would be better equipped to confidently fulfil their legal obligations to patients. It is however ultimately a pharmacist's professional responsibility that when substitution takes place, the product dispensed will be of same quality, safety and efficacy as the innovator product.[58,131] 'Dispensing doctors' and other dispensing health professionals are likewise responsible for the quality, safety and efficacy of the products they provide. A question that can then be asked is: 'What difference would it make to dispensers and consumers if the package insert indicated that a FRP had been used for purposes of registration instead of a DRP?' The consequences of providing this additional information would also have to be determined in terms of, *inter alia*, healthcare costs and adherence.

### 5.10 PAIA

The Promotion of Access to Information Act, even if technically used erroneously, proved to be useful in obtaining limited information. As neither the pharmaceutical companies nor the MCC were in fact obliged to respond to the requests, it is perhaps indicative of a sense of

'goodwill' towards the researcher, the institution or the profession that responses were obtained.

Each private company is required to have a PAIA Manual.[100,102][27] Though these manuals were not requested nor inquired about in the study, and this is a limitation of the study, it was assumed that each of the companies would have had one. The three companies that did not respond may have done so because they were of the opinion that the requests were not up to the correct PAIA standards. Their lack of response therefore does not necessarily indicate a lack of transparency and a disregard of the Act as could otherwise have been assumed. Reasons documented elsewhere for failure to respond to PAIA requests include a lack of understanding of the Act, or lack of a protocol indicating how to deal with PAIA requests.[101,102] From a layperson's perspective ('at face value') the PAIA seems to indicate that it provides 'access to information' when in fact it provides access to specified 'records'. This created an element of confusion in this study. It also makes the instrument user-unfriendly in some ways, and could even be said to not fully realise the promise in Section 32 of the Constitution of 'the right of access to information' (here not specified narrowly as 'records').

The PAIA stipulates that requests are to be sent to the CEO for private bodies. However, the direct contact details of the CEOs are sometimes extremely difficult to obtain. Few CEOs publicly disclose their contact or email addresses. This difficulty explains the delay in submitting some of the initial requests in this study. If the PAIA is to be successful in promoting the openness and transparency that it stands for, the request process could be made simpler. The Act also stipulates that a particular right to information has to be stated in the request to private bodies. This may present a challenge as the right may not be an 'official right' according to the company receiving the request. Company I for example, in its second refusal of the request indicated that a right to academic endeavour was not in their view a legitimate constitutional right which warranted the release of information. This potentially presents a limitation to the access of information for research purposes.

[27] The deadline for certain private companies to submit their manuals to the South African Human Rights Commission was extended to the 31 December, 2011, but this has subsequently again been extended to 31 December 2015. This would not have applied to the manufacturing component of the pharmaceutical industry, as they have more than 50 employees and an annual turnover of more than R10 million. See: http://www.sahrc.org.za/home/21/files/EXTENSION%20GRANTED%2030122011.pdf

The MCC in a 'General Information' Guideline (2.01 March 2011) states:

> **2.3 CONFIDENTIALITY/SECRECY**
>
> The confidentiality of information submitted to the MCC is governed by Section 34 of the Act. The MCC, committee members or staff of the Medicines Regulatory Affairs (MRA), may NOT
>
> - disclose to any person, any information acquired in the exercise of powers or performance of functions under the Act and relating to the business affairs of any person, except
>   - for the purpose of exercising his/her powers, or for the performance of his/her functions under the Act, or
>   - when required to do so by any competent court or under any law, or
>   - with the written authority of the Director-General, or
> - use such information for self-gain or for the benefit of his employer.
>
> The MCC may insist on written confirmation of the identity and affiliation of an individual inquiring telephonically, or in person, about a medicine. No information shall be disclosed telephonically unless the Medicines Control Officer knows the enquirer is entitled to receive the information. (emphasis in original)

This is why no initial informal request was submitted to the MCC and the PAIA was used as a first resort. It is also why a request for the researcher to examine the records in the Department of Health itself was not even considered. The 'Deputy Information Officer' of the Department of Health legitimately refused the erroneously worded request both times, quoting from the PAIA. The MCC's failure to furnish the PAIA Manual however is unacceptable considering that it meets the definition of a 'public body' in the Act, and in terms of Section 14 of the PAIA was required to have had a manual available within 6 months of the commencement of Section 14 (which was announced on February 15, 2002)[28]. This failure is consistent with reports on how most public or State institutions do not have PAIA Manuals.[119]

A large number of cases in which PAIA was found to have been successfully used were between companies and organisations. Political parties are also resorting to use the PAIA in significant ways.[132] The 'layperson' using the PAIA (without being trained in its use) is seemingly not as common an occurrence. While efforts have been made to increase access to PAIA by permitting its enforcement in Magistrate courts, this seems to be of no appreciable value if the 'layperson' is unable to use and apply the Act.[132]

### 5.10.1 The experience of using PAIA as a 'layperson'

Making erroneous face value use of the PAIA as a layperson (e.g. as would a pharmacist in any setting) is a major finding of this study. Although the pharmaceutical companies that responded by providing the requested information may have had a similar interpretation of

[28] Government Notice (R187), Government Gazette No. 23119. *Proclamation by President of the commencement of sections 10.14.16 & 51 of PAIA.* 15 February 2002.

the Act as the investigator, it is perhaps remarkable how much information they were prepared to voluntarily provide. It may also be assumed that the companies that did not respond to the request at all viewed the request as inappropriately worded.

When submitting an application in terms of the PAIA, clear thought needs to go into determining the 'legal right' that is being protected by the information not being in the public domain, and the details of the exact record that is required. This is problematic when a request is for a record involving the registration procedure for a medicine – as the process is already legislated as 'secret'. The forms used in the application for registration of a medicine changed from the MBR1 to the MRF1 some time after 2002. Which part of the MRF1 would a 'layperson' request? They would probably require assistance to use and apply the PAIA. How readily and freely available that assistance would be is a question in its own right. This can be highlighted as a limitation in the use of the PAIA for the 'layperson', and an obstacle in the promise of Section 32 of the Constitution. One should not need the assistance of a lawyer to use the PAIA.

**5.11 Summary**

As the MCC guidelines are providing a relatively flexible approach to generic medicines' registration, it is possible that 'irregularities' regarding tests to prove equivalence may technically not be irregularities at all. The companies may, in correspondence with the MCC, have motivated for and been granted bio-waivers. This question was not asked.

This study does not support a viewpoint that foreign reference products are not safe for use and/or cannot be used in practice. These products are, as indicated by Kanfer, prescribable and usable. They may however not be 'interchangeable' with the local innovator product and hence their use as comparators may be inappropriate. It follows that substitution of innovator products with generics registered against FRPs may then also be inappropriate. This is a potential 'gap' in the registration of generic medicines in South Africa.

The MCC has complied with WHO requirements in terms of developing and providing standards and guidelines for use in medicines registration[1] although it is acknowledged that the WHO is not itself a regulatory authority. One of the recommendations made by the WHO regarding effective medicines regulation in general is to systematically monitor the regulatory process and to identify problems. This is said to include the regulatory authority becoming a 'learning organisation'.[1] (inverted commas added) Although there may be ethical implications for the public as 'recipients' of such 'learning processes', this study highlights

some areas that may need to be clarified, and some improvements and amendments that could potentially be made.

The initial reasons for the use of generic medicines in SA (as in numerous other countries) were to help reduce the costs of healthcare. This goal was to be achieved without compromising the quality of the medicines used. The initial comparators for generic medicines were only the innovator products. Once consumers/patients are of the opinion or belief that generic medicines 'do not work', this could result in them opting for the more expensive brand products in settings where they have a choice – especially if there is a third party payer such as a medical aid. This would not reduce the cost of healthcare. Besides that, the health of consumers may be compromised. For example, sub-therapeutic concentrations from generics may result in a lack of a therapeutic effect; higher than recommended concentrations may lead to toxicity and other adverse drug reactions may be experienced. These problems may in and of themselves lead to increased healthcare costs. Some of these problems may be exacerbated because generics are no longer being registered only against innovator products; and because *in vitro* testing is being more frequently used to avoid the costs involved in *in vivo* testing.

The process in using the PAIA correctly can be easily misinterpreted without the assistance of a person trained in its use, or without oneself being trained. This study highlights some of the errors made in attempting to use the PAIA independently.

# Chapter 6: Conclusions

## 6.0 Summary of the study

The study was partly successful in meeting the objectives. The investigator was able to determine the approximate use of FRPs in the small sample of controlled release products (at least 50%). It was unsuccessful in identifying the use of FRPs and tests involved for the one BCS class IV product included as the company did not respond to the request. The study showed that for the specified sample, pharmaceutical companies were adherent to MCC guidelines and that the appropriate studies for registration were performed when required as evidenced by Table 4.3. The study succeeded in piloting the R-Score as a means of documenting the responses of the pharmaceutical companies. It could however be argued that the pharmaceutical companies would not have voluntarily provided the information they did, had it not been requested, even if erroneously, using the PAIA. As the request to the MCC for the provision of information was unsuccessful, it is not possible to validate the information provided by the pharmaceutical companies who voluntarily responded.

The action research methodology successfully enabled the investigator to obtain information, reflect on the process, modify the approach, obtain more information and to draw conclusions and recommendations from the data collected.

## 6.1 Conclusions

Should prescribers and/or dispensers know when a foreign reference product has been used to register a generic medicine? The investigator is of the opinion that the answer to this question is ‘yes’. It is evident that FRPs are being used in the registration of generic medicines as at least ten of the twenty products and possibly more used FRPs in this case study. If prescribers and dispensers do not know whether FRPs were used (and related to that, what tests were done to prove equivalence) in the registration of generic medicines, they cannot make informed choices on behalf of their patients. As it is a legal obligation of the pharmacists to implement generic substitution according to the Medicines Act, being sure of equivalence is essential in the context of legal liability. The MCC has this information. The PAIA revealed that the records are kept as hard copies by the MCC, and that an easily accessible electronic database of pertinent information for all registered medicines is not available to them.

Possible adjustments to the present system would need to include changes to the Regulations to the Medicines Act to provide for the additional proposed information about FRPs to be

included in package inserts (and possibly even the patient information leaflets – although this should be thoroughly debated first). When equivalence has been proven between a generic medicine and a reference product which is preferably the local innovator product (or a FRP that has been clinically proven to be therapeutically equivalent to the innovator product), dispensers could more confidently adhere to generic substitution as mandated in Section 22F of the Medicines Act. Dispensers' (who are pharmacists) views on the acceptability of the use of FRPs for generic medicines registration is irrelevant as the law stands, and it is possible that through anecdotal reports of certain generics 'not working', they simply avoid dispensing them.

Prescribers may choose to write 'no substitution' on their prescriptions if they are unconvinced that a generic registered against an FRP is acceptable. This could have consequences for healthcare costs.

It is debatable as to whether or not the information about registration against a FRP would be of any particular benefit to members of the public. However if patients were informed, this would fulfil the NDP requirement that patients make an 'informed decision' about the use of a particular generic product. This begs the question as to how much information a patient needs in order to make an informed decision about medicines choices – a basic understanding of pharmacology?

If comparative *in vitro* dissolution studies are on occasion being inappropriately being used alone for the registration of modified release preparations, this would be in direct contradiction with the MCC guidelines which indicate that *in vivo* bioequivalence studies are required for the registration of these preparations unless the product qualifies for a bio-waiver.

In terms of 'responsiveness', less than half of the companies voluntarily provided the full information. Of the four companies who provided all the information, two did so only after initially indicating that the information could not be disclosed. The PAIA, even in its erroneous usage, was partially effective in obtaining information from the private bodies but unsuccessful in doing so from the public body. The goal of the 'right to access of information' as stated in the Constitution that the PAIA is making provision for, has yet to be attained in South Africa in terms of medicines regulation in both private and public bodies – and not only should the access to information be revisited in terms of the PAIA, but the 'secrecy' clause of the Medicines Act may need to be reformulated.

At present, as this study demonstrates, the only option is for prescribers, dispensers and the public to rely entirely on the MCC's rigour in assessing applications for registration of modified release and other generic medicines.

### 6.2 Recommendations

- The MCC (or the new entity) should ensure that it has a PAIA manual readily available as specified in the PAIA.
- An FRP should be used as a comparator to prove equivalence of generic medicines for registration purposes as a last resort – as indicated by the MCC Pharmaceutical and Analytical guideline, and only once it has been proven to be equivalent to the local innovator product.
- If an FRP has been used to prove equivalence, consideration to making healthcare professionals, especially dispensers, (but possibly even the public) aware of this bearing in mind the possibility of unintended consequences.
- Changing patients from one generic medicine to another should not be undertaken lightly as generic medicines are not necessarily therapeutically equivalent with each other.
- The regulatory authority should ensure that guidelines for registration are strictly followed and that no 'loopholes' are possible. Some of the present guidelines should possibly be reformulated as regulations to the Medicines Act.
- A culture of openness and transparency must be developed in both the regulatory authority and in pharmaceutical companies. The transparency does not need to be restricted to the use of FRPs only but also to the general functioning of these bodies.
- The regulatory authority should ensure that all relevant records are captured electronically so that information can be more efficiently accessed by both it and those who request information.

### 6.3 Possible future areas of research

It would not be feasible (or reasonable) as stated by the DIO to take the MCC to court for their refusal to provide the requested information. Relatively good information can be obtained through having a parliamentary question asked – provided a member of parliament can be found who is prepared to ask it, and that the Member of Parliament asking the question formulates it correctly. Unfortunately the present party political system in South Africa makes it difficult to find individual (independent) members of parliament who are willing to ask parliamentary questions.

Research to establish the extent of the use of FRPs as comparators in the registration of generic medicines could be undertaken and the extent to which the FRPs have or have not been shown to be therapeutically equivalent to the innovator products. This research should include BCS class IV products.

Research documenting problems, adverse drug reactions or effects that arise from the use of generics registered using FRPs would be useful. Anecdotal reports from patients, prescribers and dispensers of generic medicines that 'don't work' could be used as a starting point. Such studies could document the actual effects (efficacy and effectiveness) of generics registered using a FRP comparator rather than the IP or even a DRP as comparator. A similar study could compare the therapeutic effectiveness and *in vivo* bioavailability between a group of patients receiving an innovator product, a group receiving a generic registered using the IP as a comparator and a group receiving a generic registered using a FRP as a comparator. Dissolution profiles for these three products could also be assessed and compared.

It might be of interest to determine patients' responses to knowing about generic medicines being registered using FRPs and if they would still choose to be substituted onto them even if the costs are reduced. Could knowing about FRPs have an adverse effect on adherence (compliance)? Pharmacists or dispensers could also be asked about their views or their perceptions of the risks of substituting a patient onto a generic medicine that may not have been proven to be equivalent to the local innovator product.

Finally, a 'layperson's' use of PAIA is not as straight forward as it would appear at face value. The fact that most of the companies approached were nevertheless prepared to provide relatively sensitive information is perhaps a tentative indicator that pharmaceutical companies are prepared to contribute to academic research in South Africa. The question remains however as to whether or not the companies would have responded had the requests for information not been asked using the PAIA. The fact that useful information was obtained even using the PAIA incorrectly possibly indicates that the PAIA is in and of itself a valuable tool.

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# Appendices

# Appendix 1: List of medicines that require data other than comparative dissolution data from circulars 14/89 and 14/95

**MEDICINES CONTAINING THE FOLLOWING CHEMICAL ENTITIES, CERTAIN COMBINATIONS, SPECIFIC GROUPS OF ENTITIES OR MEDICINES FALLING INTO A SPECIFIC PHARMACOLOGICAL GROUP, WHICH WILL USUALLY REQUIRE DATA OTHER THAN COMPARATIVE DISSOLUTION DATA AS EVIDENCE OF EFFICIACY**

Additions and deletions to the following list may be made by Council from time to time

Acetyldigitoxin
Acetyl furazole
N-Acetylprocainamide
Alseroxylon
Amiodarone
Antibiotics (unless otherwise determined by Council)
Benzthiazide
Benzoylpas calcium
Butalbital, aspirin, phenacetin, caffeine
Carbamezepine
Carisoprodol, phenacetin, caffeine (with or without codeine)
Cephalosporins
Chlorambucil
Chlorpromazine
Conjugated oestrogens with meprobamate
Cyclosporin A
Cytotoxic agents
Deserpidine
Deserpidine and hydrochlorothiazide
Deserpidine and methyclothiazide
Dicoumarol
Dienoestrol
Digoxin
Disopyramide
Doxycycline
Erythromycin (base and eters)
Ethinyl oestradiol
Ethotoin
Ethoxzolamide
Fludrocortisone acetate
Fluprednisolone
Guanethidine sulphate
Hydrallazine hydrochloride and hydrochlorothiazide
Hydrallazine hydrochloride and reserpine
Hydrocortisone acetate
Hydroxyzine pamoate
Isoproterenol sublingual
Liothyronine sodium
Lithium compounds
Menadione
Methdilazine
Methocarbamol with aspirin
Methyltestosterone
Minocycline
Oxtriphylline (choline theophyllinate)
PAS
PAS calcium
PAS potassium
PAS sodium
PAS and isoniazid
PAS sodium and isoniazid
Paramethadione
Paramethasone acetate
Phenobarbitone
Phenylaminosalicylate
Phenytoin
Phytonadione
Procainamide
Prochlorperazine
Promazine
Promethazine
Quinethazone
Quinidine
Quinidine polygalacturonate
Rauwolfia Serpentina
Rescinnamine
Reserpine
Reserpine and chlorothiazide
Reserpine and hydrochlorothiazide
Reserpine and hydrallazine
Reserpine, hydrallazine hydrochlorothiazide and hydrochlorothiacide
Reserpine and hydroflumethiazide
Reserpine and trichlormethiazide
Sodium sulfoxone
Spironolactone
Spironolactone and hydrochlorothiazide
Stilboestrol
Stilboestrol diphosphate
Sulfoxone sodium
Sulphadiazine sodium bicarbonate
Sulphadiazine, sulphadimidine and sulphamerazine
Sulphadimethoxine
Sulphafurazole
Sulphamethoxypyridazine acetyl
Sulphaphenazole
Sulphasomidine
Theophylline
Theophylline sodium glycinate
Thioridazine
Thyroglobulin
Tretamine
Trifluoperazine
Triflupromazine
Trimeprazine
Uramustine
Warfarin, sodium and potassium

# Appendix 2: Request to pharmaceutical companies

Faculty of Pharmacy
Rhodes University
P.O Box 94
Grahamstown, 6140

[Date]

The Chief Executive Officer/ Information Officer
[Address]

***Our ref: 0001/xxx/2011***

Dear

**REQUEST FOR INFORMATION IN TERMS OF THE PROMOTION OF ACCESS TO INFORMATION ACT REGARDING THE REGISTRATION OF GENERIC MEDICINES.**

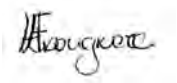
My name is Eldinah Hwengwere. I am a student in the Faculty of Pharmacy at Rhodes University. I am studying towards a Masters degree. Please find attached a completed **FORM C** request for access to information as outlined in the Promotion of Access to Information Act 2 of 2000 (PAIA). In summary I would like to find out whether a Foreign Reference Product was used in the registration process of the following product which is manufactured and/or distributed by your company:

- List of products

I acknowledge the secrecy clause of section 34 of the Medicines and Related Substances Act. I am also aware that a fee is usually required, but am requesting exemption from payment on the basis of being a full time student and that the information will be used for academic and scholarly purposes only. I have attached to this letter a copy of my registration as a student and a signed letter from my supervisor.

As recommended by the PAIA, please use the above reference number (0001/XXX/2011) in future correspondence. If there is any information that you are unable to provide, please could you give reasons as to why not. I am also in the process of applying for similar information from the MCC using the PAIA.

Yours Faithfully



Eldinah Hwengwere

# FORM C

## REQUEST FOR ACCESS TO RECORD OF PRIVATE BODY

(Section 53(1) of the Promotion of Access to Information Act, 2000) (Act. No. 2 of 2000)

**[Regulation 10]**

**A. Particulars of private body**

The Head:

**CEO name and company address**

**B. Particulars of person requesting access to the record**

*(a) The particulars of the person who requests access to the record must be given below.*
*(b) The address and/or fax number in the Republic to which the information is to be sent must be given.*
*(c) Proof of the capacity in which the request is made, if applicable, must be attached.*

Full names and surname: **ELDINAH HWENGWERE**

Identity number: **AN372419** (passport)

Postal Address:
**FACULTY OF PHARMACY**
**RHODES UNIVERSITY**
**P.O BOX 94,**
**GRAHAMSTOWN. 6140**

Fax Number: **0466361205**
Telephone number: **0729298387**
E-mail Address: g06h3782@campus.ru.ac.za

Capacity in which the request is made, when made on behalf of another person: **N/A**

**C. Particulars of person on whose behalf request is made**

*This section must be completed ONLY ifs requests for information is made on behalf of another person.*

Full names and surname: _____
Identity number: _____

**D. Particulars of record**

*(a) Provide full particulars of the record to which access is requested, including the reference number if that is known to you, to enable the record to be located.*
*(b) In the provided space is inadequate, please continue on a separate folio and attach it to this form.*

***The requester must sign all the additional folios.***

1. Description of record or relevant part of the record:

   **COULD YOU PLEASE INFORM ME WHAT TESTS WERE DONE TO SHOW BIOEQUIVALENCE FOR REGISTRATION OF THE ATTACHED LIST OF GENERIC (MULTISOURCE INTERCHANGEABLE) MEDICINES, MANUFACTURED AND/OR DISTRIBUTED BY YOUR COMPANY AND PLEASE STATE WHETHER A DOMESTIC OR FOREIGN REFERENCE PRODUCT WAS USED.**

2. Reference number, if available:

3. Any further particulars of record:

**E. Fees**

*(a) A request for access to a record, other than a record containing personal information about yourself, will be processed only after a request fee has been paid.*
*(b) You will be notified of the amount required to be paid as the request fee.*
*(c) The fee payable for access to a record depends on the form in which access is required and the reasonable time required to search for and prepare a record.*
*(d) If you qualify for exemption of the payment of any fee, please state the reason for exemption.*

Reason for exemption from payment of fees:

**INFORMATION IS TO BE USED FOR ACADEMIC AND SCHOLARLY PURPOSES ONLY.**

**F. Form of access to record**

*If you are prevented by a disability to read, view or listen to the record in the form of access provided for in 1 to 4 hereunder, state your disability and indicate I which form the record is required.*
Disability: **N/A**

**G. Particulars of right to be exercised or protected**

*If the provided space is inadequate, please continue on a separate folio and attach it to this form. The requester must sign all the additional folios*

1. Indicate which right is to be exercised or protected.

   **THE RIGHT OF ACCESS TO INFORMATION, AND THE RIGHT OF ACADEMIC AND SCHOLARLY ENDEAVOUR.**

2. Explain why the record requested is required for the exercise or protection of the aforementioned right

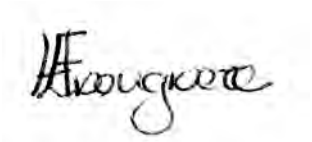
   **THIS FORMS PART OF A POSTGRADUATE MASTERS DEGREE BY THESIS AT RHODES UNIVERSITY.**

**H. Notice of decision regarding request for access:**

*You will be notified in writing whether your request has been approved / denied. If you wish to be informed in another manner, please specify the manner and provide the necessary particulars to enable compliance with your request.*

How would you prefer to be informed of the decision regarding your request for access to the record? **PLEASE EMAIL ME THE INFORMATION AT:** g06h3782@campus.ru.ac.za

Signed at **GRAHAMSTOWN** this **30th** day of **May 2011**

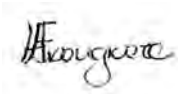


SIGNATURE OF REQUESTER

## Name of company:

| **Trade name of product** | **Chemical Entity** | **FRP used for registration?** *(yes/no)* | **Test(s) done to show equivalence with reference product for purposes of registration in SA** |
|---|---|---|---|
| List of product(s) | Name of active pharmaceutical ingredient | | |

Our ref: 0001/xxx/2011 (as in cover letter)



# Appendix 3: First request to the MCC

Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown. 6140

24 May 2011

Registrar of Medicines
Medicines Control Council
Private Bag X828
Pretoria. 0001

***Our ref: 0001/MCC/2011***

Dear Mrs Hela

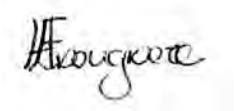
**REQUEST FOR INFORMATION IN TERMS OF THE PROMOTION OF ACCESS TO INFORMATION ACT REGARDING THE REGISTRATION OF GENERIC MEDICINES.**

My name is Eldinah Hwengwere. I am a student in the Faculty of Pharmacy at Rhodes University. I am studying towards a Masters degree. Please find attached a completed **FORM A** request for access to information as outlined in the Promotion of Access to Information Act 2 of 2000 (PAIA). I am interested in the use of foreign reference products in the registration of generic medicines. I noted that the Minister of Health did not address this question when it was asked in parliament. (Question No 3021 - Internal Question Paper: 29 October 2010). The question was asked in relation to generic medicines registration 'how many were used [registered] against foreign reference products as opposed to local innovator products?' The answer given was that the MCC does not use generic products for comparative purposes. It appears as if there may have been a misunderstanding of what a foreign reference product is, and I would like to ask this question again, as well as to ask whether a set of twenty specific products were or weren't registered using a foreign reference product.

I acknowledge the secrecy clause of section 34 of the Medicines and Related Substances Act. I am however requesting this information in the public's best interest. The information I hope to receive from you/MCC will be used strictly for academic purposes. I have attached to this letter a copy of my registration as a student and a signed letter from my supervisor.

As recommended by the PAIA, please use the above reference number (0001/MCC/2011) in future correspondence. If there is any information that you are unable to provide, I would appreciate your guidance in finding other sources from which the information could be made available. I will in any case be contacting the individual manufacturers.

Yours Faithfully



Eldinah Hwengwere

**FORM A**

**REQUEST FOR ACCESS TO RECORD OF PUBLIC BODY**

(Section 18 (1) of the Promotion of Access to Information Act, 2000

(Act No. 2 of 2000)

**[Regulation 2]**

FOR DEPARTMENTAL USE

Reference number:_____

**Request received by:_____**

(state rank, name and surname of information officer/deputy information officer) on _____(date) at_____ (place).

Request fee (if any): R…….

Deposit fee (if any): R…….

Access fee: R…….

_____

SIGNATURE OF INFORMATION OFFICER/DEPUTY INFORMATION OFFICER

**A. Particulars of public body**

**MEDICINES CONTROL COUNCIL**

**PRIVATE BAG X828**

**PRETORIA**

**0001**

**B. Particulars of person requesting access to the record**

*(a) The particulars of the person who requests access to the record must be recorded below.*
*(b) Furnish an address and/or fax number in the Republic to which information must be sent*
*(c) Proof of the capacity in which the request is made, if applicable, must be attached.*

Full names and surname: **ELDINAH HWENGWERE**

Identity/Passport number: **AN372419**

Postal address**:** **FACULTY OF PHARMACY, RHODES UNIVERSITY, PO BOX 94, GRAHAMSTOWN. 6140**

Fax number: **0466361205**

Telephone number: **0729298387**

E-Mail Address **g06h3782@campus.ru.ac.za**

Capacity in which request is made, when made on behalf of another person: **N/A**

**A. Particulars of person on whose behalf request is made**

*This section must be completed ONLY if a request for information is made on behalf of another person.*

Full names and surname:

Identity number:

**D. Particulars of record**

*(a) Provide full particulars of the record to which access is requested, including the reference number if that is known to you, to enable the record to be located.*
*(b) If the provided space is inadequate please continue on a separate folio and attach it to this form.* ***The requester must sign all the additional folios****.*

1. Description of record or relevant part of the record:

**i. HOW MANY GENERIC MEDICINES WERE REGISTERED AGAINST FOREIGN REFERENCE PRODUCTS BETWEEN 2007 AND 2010 AS OPPOSED TO BEING REGISTERED AGAINST LOCAL INNOVATOR PRODUCTS? [PLEASE NOTE THAT THIS QUESTION WAS INCORRECTLY ANSWERED IN THE**

**PARLIAMENTARY INTERNAL QUESTION PAPER NO 34, QUESTION 3021, 29 OCTOBER 2010.]**

ii. **COULD YOU PLEASE INFORM ME WHAT TESTS WERE DONE TO SHOW BIOEQUIVALENCE FOR REGISTRATION OF THE ATTACHED LIST OF 20 GENERIC (MULTISOURCE INTERCHANGEABLE) MEDICINES, AND FOR EACH, WHETHER A DOMESTIC OR FOREIGN REFERENCE PRODUCT WAS USED.**

2. Reference number, if available:

3. Any further particulars of record:

**E. Fees**

| | |
|---|---|
| *(a)* | *A request for access to a record, other than a record containing personal information about yourself, will be processed only after a request fee has been paid.* |
| *(b)* | *You will be notified of the amount required to be paid as the request fee.* |
| *(c)* | *The **fee payable for access** to a record depends on the form in which access is required and the reasonable time required to search for and prepare a record.* |
| *(d)* | *If you qualify for exemption of the payment of any fee, please state the reason for exemption.* |

Reason for exemption from payment of fees**:** **I DO NOT EARN A SALARY.**

**F**. **Form of access to record**

| *If you are prevented by a disability to read, view or listen to the record in the form of access provided for in 1 to 4 hereunder, state your disability and indicate in which form the record is required.* | |
|---|---|
| Disability: _____<br><br>_____ | Form in which record is required: _____<br><br>_____ |

*Mark the appropriate box with an **'X'**.*

*NOTES:*

*(a) Your indication as to the required form of access depends on the form in which the record is available.*

*(b) Access in the form requested may be refused in certain circumstances. In such a case you will be informed if access will be granted in another form.*

*(c) The fee payable for access to the record, if any, will be determined partly by the form in which access is requested.*

**1. If the record is in printed form:**

| | | | |
|---|---|---|---|
| | Copy of record* | | Inspection of record |

**2. If record consists of visual images:**

(this includes photographs, slides, video recordings, computer-generated images,sketches, etc).

| | | | | | |
|---|---|---|---|---|---|
| | view the images | | copy of the images* | | transcription of the images* |

**3. If record consists of recorded words or information which can be reproduced in sound:**

| | | |
|---|---|---|
| | Listen to the soundtrack (audio cassette) | transcription of soundtrack*<br>(written or printed document) |

| | | | | | |
|---|---|---|---|---|---|
| **4. If record is held on computer or in an electronic or machine – readable form:** | | | | | |
| | Printed copy of record* | | Printed copy derived from the record* | | copy in computer readable form*(stiffy or compact disc) |

| | | |
|---|---|---|
| ***** If you requested a copy or transcription of a record (above), do you wish the copy or transcription to be posted to you?<br><br>**A postal fee is payable.** | YES | NO |
| *Note that if the record is not available in the language you prefer, access may be granted in the language in which the record is available.* | | |
| In which language would you prefer the record? | | |

**A. Notice of decision regarding request for access**

| |
|---|
| You will be notified in writing whether your request has been approved/denied. If you wish to be informed thereof in another manner, please specify the manner and provide the necessary particulars to enable compliance with your request. |

How would you prefer to be informed of the decision regarding your request for access to the record? **PLEASE EMAIL ME THE INFORMATION AT** g06h3782@campus.ru.ac.za

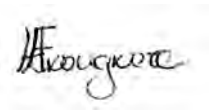
Signed at **GRAHAMSTOWN** this **the 24th** day of **MAY** **2011**

SIGNATURE OF REQUESTER

1. How many generic medicines were registered against foreign reference products between 2007 and 2010 as opposed to being registered against local innovator products? [Please note that this question was incorrectly answered in the parliamentary internal question paper no 34, question 3021, 29 October 2010.]

2. Please fill in the following table:

| **Product Trade Name** | **Chemical Entity** | **Manufacturer** *(Holder of certificate of registration of product)* | **Foreign product used?** | **Tests done to show equivalence with reference product for purposes of registration** |
|---|---|---|---|---|
| List of 20 products | Specific active ingredient in product | Companies for each respective product | | |



# Appendix 4: Parliamentary Question

*QUESTION NO. 3021*

*DATE OF PUBLICATION IN INTERNAL QUESTION PAPER: 29 October 2010 *

*(INTERNAL QUESTION PAPER NO. 34)*

*Mrs J F Terblanche (DA) to ask the Minister of Health:*

(1) Whether any generic medicines were registered (a) in (i) 2007,(ii) 2008 and (iii) 2009 and (b) since 1 January 2010; if so, (aa) how many in each case, (bb) how many were used against foreign reference products as opposed to local innovator products and (cc) what percentage of total registrations in each specified period were generic medicines;

(2) How many new chemical entities were registered in each specified period?

**REPLY**

(1) Yes

(a), (b), (aa) and (cc): The following table reflects the details in this regard

| **Year** | **Number of generic medicines registered** | **Percentage of total registration** |
|---|---|---|
| 2007 | 359 | 92.76 |
| 2008 | 434 | 89.85 |
| 2009 | 472 | 90.42 |
| 2010 (October) | 283 | 92.33 |

(bb) MCC does not use generic products for comparative purposes.

(2) The following table reflects details in this regard

| **Year** | **Number of new chemical entities registered** |
|---|---|
| 2007 | 7 plus 12 various strengths |
| 2008 | 12 plus 11 various strengths |
| 2009 | 14 plus 20 various strengths |
| 2010 (1 October) | 9 plus 4 various strengths |

# Appendix 5: Letter sent to unresponsive companies

Faculty of Pharmacy
Rhodes University
P.O Box 94
Grahamstown, 6140

19 August 2011

The Chief Executive Officer/ Information Officer

[Address]

***Our ref: 0001/XXX/2011***

Dear [Name]

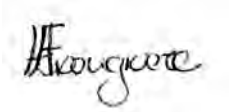
**REQUEST FOR INFORMATION IN TERMS OF THE PROMOTION OF ACCESS TO INFORMATION ACT REGARDING THE REGISTRATION OF GENERIC MEDICINES.**

As indicated in previous correspondence dated 1 June 2011, my name is Eldinah Hwengwere and I am a postgraduate student at Rhodes University. You acknowledged the receipt of my request but I have not yet received a response to the request in terms of the Promotion of Access to Information Act (Act 2 of 2000). According to Section 56 of the Act, a response to a request must be given within 30 days. For your convenience this section is quoted below.

> **Decision on request and notice thereof**
>
> **56.** (1) Subject to Chapter 5 of this Part, the head of the private body to whom the request is made **must, as soon as reasonably possible, but in any event within 30 days, after the request has been received** or after the particulars required in terms of section 53(2) have been received—
>
> (a) decide in accordance with this Act whether to grant the request; and
> (b) notify the requester of the decision and, if the requester stated, as contemplated in section 53(2)(e), that he or she wishes to be informed of the decision in any other manner, inform him or her in that manner if it is reasonably possible.

I believe I have provided all the particulars required by section 53(2) but I would be happy to elaborate more fully on my request should that be needed in order for you to make a decision about my request. In terms of section 53(2)(e) I requested that I be informed by email.
I have to the best of my knowledge met all the requirements of the application I have made. I am however also attaching an undertaking of confidentiality for your information. I am therefore requesting your official response to my formal application for information dated 1 June 2011.

Kind regards



Eldinah Hwengwere

# Appendix 6: Confidentiality undertaking

RHODES UNIVERSITY
Grahamstown • 6140 • South Africa

FACULTY OF PHARMACY
Tel: 046 603 8381 • Fax: 046 636 1205
P O Box 94, Grahamstown, 6140
e-mail: dean.pharmacy@ru.ac.za

**Confidentiality undertaking**

I, Eldinah Hwengwere am a Masters student at Rhodes University, Grahamstown. I am conducting research on the use of foreign reference products in South Africa for the purposes of registration of generic/multi source products. I have approached your company for information regarding the registration of some of your generic products. The information that will be provided is strictly for my research for my Masters degree.

I undertake not to disclose the name of your company or the name of the generic products used in the study. Pseudonyms have been devised to refer to companies and the products for purposes of publication in order to protect the interests of the participant companies. I can make these pseudonyms available on request.

Signed at: GRAHAMSTOWN Date: 19 August 2011

Student: Eldinah Hwengwere

Supervisor: Professor Roy Jobson

Dean of Faculty of Pharmacy: Professor R. B. Walker

# Appendix 7: List of codes designated to companies and products

| Company | Products | Pharmacological nature of API |
|---|---|---|
| A | A1 | Affects bone metabolism |
| B | B1 | Anti-cholesterol |
| | B2 | Vasodilator |
| | B3 | Anti-depressant |
| C | C1 | Anti-epileptic |
| | C2 | Anti-hypertensive |
| | C3 | Anti-hypertensive |
| | C4 | Mineral supplement |
| | C5 | Analgesic |
| | C6 | Anti-arrhythmic |
| D | D1 | Analgesic |
| E | E1 | Antibiotic |
| F | F1 | Anti-inflammatory |
| G | G1 | Anti-arrhythmic |
| | G2 | Anti-inflammatory |
| | G3 | Anti-epileptic |
| H | H1 | Anti-hypertensive |
| I | I1 | Anti-obesity |
| | I2 | Anti-epileptic |
| | I3 | Alpha-adrenoreceptor antagonist |

# Appendix 8: Company F – Second response

13 July 2011

Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown, 6140

**Ref: 0001/ 2011 – Request for information regarding the registration of generic medicines**

Dear Eldinah Hwengwere,

Herewith a response to your additional request:

In line with the guidelines for the registration of medicines published and distributed by the MCC (www.mccza.com), a solid oral dosage form such as a tablet or capsule will require bioequivalence studies as proof of comparative efficacy with the innovator unless a biowaiver can be supported.

It is also a requirement of these guidelines, that if a foreign reference product is used in such studies, equivalence must be demonstrated between the study product, the foreign reference product, and a product registered in South Africa containing the same API. This equivalence will usually be confirmed by dissolution testing.

As such, if a foreign reference product was used in the registration of a generic medicine, it follows that both a bioequivalence and dissolution study has been conducted.

Going forward with your research, as a suggestion; a familiarity with the guidelines relevant to the topic you are investigating will aid you greatly in understanding the information you are requesting and assimilating.

Kindly provide an original signature below, and return to acknowledge receipt.

Thank you and kind regards,

Regulatory Pharmacist

Received by: Eldinah Hwengwere Sign: Hwengwere Date: 14/07/2011

# Appendix 9: Company I – Final refusal

22 September 2011

**Ms Eldinah Hwengwere**
**Faculty of Pharmacy**
**Rhodes University**
**PO. Box 94**
**Grahamstown, 6140**

*Your ref: 0001/ 2011*

Dear Ms Hwengwere

**REQUEST FOR INFORMATION IN TERMS OF THE PROMOTION OF ACCESS TO INFORMATION ACT REGARDING THE REGISTRATION OF GENERIC MEDICINES**

Your letter dated 19 August 2011 has reference.

As stated in our previous correspondence of 3 June 2011, we reserved our right to comment on the validity of your request in terms of Act 2 of 2000. We have been advised that your request is not consistent with the intention of the Act, nor does it conform to the requirements of the Act as you, inter alia, fail to explain which rights you are exercising or protecting as:

a) the right of Access to Information cannot on its own, within the context of the Act, grant you access to our or any other private body's records. In this respect we refer you to Section 32 of the Constitution which clearly stipulate the intention of this right;

b) the right, "academic and scholarly endeavour" (as recorded in your initial request) is not a recognised right in terms of the Constitution.

# Appendix 10: MCC First refusal

health
Department:
Health
REPUBLIC OF SOUTH AFRICA


Telephone : (012) 395-8457
Fax : (012) 395 - 8489
E-mail address wissing@health.gov.za

Enquiry Mr G J Wissing
Cluster: Legal Services
Private Bag X828
PRETORIA, 0001
Reference C10/26


Ms Eldirah Hwengwere
Faculty of Pharmacy
Rhodes University
PO Box 94
GRAHAMSTOWN
6140

Dear Ms Hwengwere

**REQUEST FOR ACCESS TO INFORMATION IN TERMS OF THE PROMOTION OF ACCESS TO INFORMATION ACT, 2000**

1 The above matter refers.

2. Your request to access the information mentioned in Part D of the prescribed form that you completed and submitted to the Department of Health has been considered in terms of the Promotion of Access to Information Act, 2000 (Act No. 2 of 2000) ("the Act"). Access to the requested records has been refused for the following reasons.

3. Request 1: The Registrar of Medicines disputes that the parliamentary question was incorrectly answered. The question was: 'Whether any generic medicines were registered (a) in (i) 2007, (ii) 2008, and (iii) 2009 and (b) since 1 January 2010; if so, (aa) how many in each case, (bb) how many were used against foreign reference products as opposed to local innovator products and (cc) what percentage of total registrations in each specified period were generic medicines"

—

"The MCC DOES NOT USE GENERIC PRODUCTS FOR COMPARATIVE PURPOSES"
The Registrar is of the opinion that the question was correctly answered. The question was not "how many generic medicines were registered against foreign reference products as against local innovator products".

The MCC register does not indicate how a product was evaluated. Such information is in the product files which are currently in hard copies. The MCC does not have the resources to go through each file for the years cited to establish whether the reference product was a local innovator or not. Your request is therefore refused in terms of section 45(b) of the Act.

Request 2: The information you requested falls within the ambit of section 36 of Act. We suggest you contact the respective companies with a similar request in terms of the Promotion of Access to Information Act, 2000, for the information.

4. We trust that you find the above in order.

Regards

**MR G J WISSING**
**DEPUTY INFORMATION OFFICER**
**DATE:** 13/07/11

# Appendix 11: MCC Internal appeal

Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown, 6140

05 September 2011

Registrar of Medicines
Medicines Control Council
Private Bag X828
Pretoria. 0001

***Our ref: 0001/MCC/2011***

Dear Mrs Hela

**INTERNAL APPEAL: REQUEST FOR INFORMATION IN TERMS OF THE PROMOTION OF ACCESS TO INFORMATION ACT REGARDING REGISTRATION OF GENERIC MEDICINES.**

1. As indicated in my previous communication, dated 24 May 2011, my name is Eldinah Hwengwere and I am a Masters student at Rhodes University. My request for Information regarding the use of foreign reference products and the tests involved to prove equivalence for the registration of generic products was refused. I am therefore making a formal Internal Appeal in terms of Section 74 of the Promotion of Access to Information Act (Act 2 of 2000).

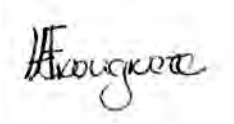
2. I would also like to request a copy in terms of Section 14(3) of the Promotion of Access to Information Act, (Act 2 0f 2000) of the MCC's Information Manual (which is required to have been compiled in terms of Section 14 (1) of the Promotion of Access to Information Act, (Act 2 of 2000). Please may I have the copy sent to me electronically at: g06h3782@campus.ru.ac.za

I have attached to this letter; the prescribed Form B which outlines my grounds for appeal and relevant annexures i.e. the initial request and the response I received refusing my request. As can be seen from the date of the refusal 13/07/2011 my appeal falls well within the 60 days required by Section 75(1)(a)(i) of the Act.

As no fee was required for my initial request, because I am a student, I am assuming that no fee will be required for this appeal.

I look forward to your response.

Kind regards



Eldinah Hwengwere

# FORM B

## NOTICE OF INTERNAL APPEAL

(Section 75 of the Promotion of Access to Information Act, 2000 (Act No. 2 of 2000))

**[Regulation 8]**

Reference Number: **0001/MCC/2011**

### A. Particulars of public body

The Information Officer:

**MRS HELA**

**MEDICINES CONTROL COUNCIL**

**PRIVATE BAG X828**

**PRETORIA**

### B. Particulars of requester/third party who lodges the internal appeal

*(a) The particulars of the person who is lodging the internal appeal, must be completed below.*

*(b) Proof of the capacity in which appeal is lodged, if applicable, must be attached.*

*(c) If the appellant is a third person and not the person who originally requested the information, the particulars of the requester must be stated at C below.*

| | |
|---|---|
| Full names and surname | : **ELDINAH HWENGWERE** |
| Identity number | : **AN372419 (passport)** |
| Postal address | : **FACULTY OF PHARMACY, RHODES UNIVERSITY, P.O.BOX 94, GRAHAMSTOWN, 6140** |
| Fax number | : **0466361205** |
| Telephone number | : **0729298387** |
| E-mail address | : g06h3782@campus.ru.ac.za |

Capacity in which an internal appeal on behalf of another person is lodged: **N/A**

## C. Particulars of requester

| |
|---|
| *This section must be completed ONLY if a third party (other than the requester) is lodging the internal appeal.* |

Full names and surname : ……..

Identity number : ……..

## D. The decision against which the internal appeal is lodged

| |
|---|
| *Mark the decision against which the internal appeal is lodged with an 'X' in the appropriate box:* |

| | |
|---|---|
| **X** | Refusal of request for access. |
| | Decision regarding fees determined in terms of section 22 of the Act. |
| | Decision regarding the extension of the period within which request must be dealt with in terms of section 26(1) of the Act. |
| | Decision in terms of section 29(3) of the Act to refuse access in the form as requested by the requester. |
| | Decision to grant request for access. |

## E. Grounds for appeal

| |
|---|
| If the provided space is inadequate please continue on a separate folio and attach it to this form. **You must sign all the additional folios**. |

State the grounds upon which the internal appeal is based:

**PLEASE FIND GROUNDS FOR INTERNAL APPEAL ATTACHED AS ANNEXURE A**

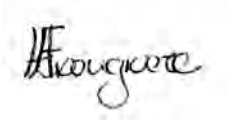
## F. Notice of decision on appeal

| |
|---|
| You will be notified in writing of the decision on your internal appeal. If you wish to be informed thereof in another manner, please specify the manner and provide the necessary particulars to enable compliance with your request**.** |

State the manner: **PLEASE GIVE A WRITTEN RESPONSE THROUGH EMAIL**

Particulars of manner: g06h3782@campus.ru.ac.za

Signed at: **GRAHAMSTOWN** this **29th** day of **August** of **2011**



SIGNATURE OF APPELLANT

## Annexure A

FOR DEPARTMENTAL USE:

OFFICIAL RECORD OF INTERNAL APPEAL:

Appeal received on (date) by (state rank, name and surname of information officer/deputy information officer).

Appeal accompanied by the reasons for the information officer/deputy information officer's decision and, where applicable, the particulars of any third party to whom or which the records, submitted by information officer/deputy information officer on (date) to the relevant authority.

OUTCOME OF APPEAL:

DECISION OF INFORMATION OFFICER/DEPUTY INFORMATION OFFICER CONFIRMED/SUBSTITUTED BY NEW DECISION

NEW DECISION:

DATE RELEVANT AUTHORITY

DATE RECEIVED BY THE INFORMATION OFFICER/DEPUTY INFORMATION OFFICER FROM THE RELEVANT AUTHORITY:

# Grounds for Internal Appeal

## Appeal Pursuant to the Promotion of Access to Information Act, Act 2 of 2000

The appellant is Eldinah Hwengwere and this appeal is directed to the Registrar of the Medicines Control Council (MCC). The Registrar is the relevant authority in terms of Section 74 of the Promotion of Access to Information Act (PAIA) to decide an appeal. On the 24th of May, the appellant made a formal request in terms of PAIA to the MCC. The request was for records relating to the reference products and tests involved in establishing equivalence of generic medicines for purposes of registration. A copy of this request is attached to this appeal and is marked as Annexure B.

In a letter dated 13/07/2011, the MCC's Deputy Information Officer, Mr. G J Wissing, wrote to the appellant to advise that the request had been refused in terms of Section 45(b) of PAIA. A copy of this letter is annexed to this appeal as Annexure B. The appellant does not accept the reasons given as adequate grounds for refusal and submits this appeal to the Registrar in terms of Section 74 of PAIA.

The appellant contends that Section 45(b) of PAIA is not a valid basis for refusing this request for the following reasons:

1. It is not unreasonable to anticipate that the Regulatory Authority should be able to access the product files of any product at any given time.

2. Section 15(7) of the Medicines and Related Substances Act (Act 101 of 1965) states that:

   **Any registration under this section, including the registration of medicines already registered . . . may be made subject to such conditions as may with regard to the succeeding provisions of this section be determined by the council.**

   As every medicine is registered with 'conditions of registration' it must mean that should any query about the basis for a particular condition of registration be raised, the MCC can at any time access the product files (dossier) of a medicine's application. Accessing the product files would therefore surely be a normal part of the regulatory authority's everyday activities and Section 45(b) of the PAIA (Act 2 of 2000) would not apply. For example, a standard set of conditions which accompany a certificate of registration would include the following:

   - The applicant shall ensure that the medicine is manufactured and controlled in terms of the current Good Manufacturing Practices as determined by the Council
   - The manufacture of this medicine is subject to regular investigation and inspections by the inspectors appointed in terms of Section 26 of the Act, to assess compliance with current Good Manufacturing Practices.
   - The information in the package insert shall be updated on a regular basis to conform to the package insert recently approved by the Council.
   - The applicant must comply with all the legal requirements of the Medicines and Related Substances Act, 1965 (Act 101 of 1965).
   - The registration of this medicine shall be subject to review at intervals as determined by Council regarding its quality, safety and efficacy, and the registration of this medicine may be varied subject to issues Council may deem fit.
   - The first two production batches must be fully validated in terms of the detailed process validation protocol submitted at the time of the application for registration, and the validation report must be submitted within a month after completion of validation.

3. Section 15(7) of the Medicines and Related Substances Act, (Act 101 of 1965) mentioned above is further supported by Regulations 23(1)(j) and 26(1)(10) of the Medicines and Related Substances Act 101 of 1965. The Regulatory Authority should surely be able at any time to verify the reasons for any conditions of registration

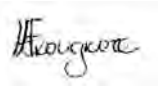
1. Section 46 of PAIA indicates that disclosure of information is a requirement if the information is in the public's best interest, see below:

   **46. Despite any other provision of this Chapter, the information officer of a public body must grant a request for access to a record of the body contemplated in section 34(1), 36(1), 37(1)*(a)* or *(b)*, 38*(a)* or *(b)*, 39(1)*(a)* or *(b)*, 40, 41(1)*(a)* or *(b)*, 42(1) or (3), 43(1) or (2), 44(1) or (2) or 45, if—**
   ***(a)* the disclosure of the record would reveal evidence of—**
   **(i) a substantial contravention of, or failure to comply with, the law; or**
   **(ii) an imminent and serious public safety or environmental risk; and**
   ***(b)* the public interest in the disclosure of the record clearly outweighs the harm contemplated in the provision in question.**

   In general, it is in the public's best interest for prescribers and dispensers to know which generics have been registered against a Domestic Reference Product (DRP) and which generics have been registered against a Foreign Reference Product (FRP). This is particularly important in view of Section 22F(1)(b) of the Act which mandates the dispensing of generic medicines. It is important information for prescribers in terms of Section 22F(4)(a) of the Act who may not wish to have a generic registered against a foreign reference product dispensed.

2. The selected companies have already been approached to participate in the study by responding to the same questions posed to the Council. However validation of the responses given will come from the information received from the Council.

3. The names of the companies and products involved in the study have been assigned pseudonyms to conceal their identities in all publications



# Appendix 12: MCC Second refusal

health

Department:
Health
REPUBLIC OF SOUTH AFRICA


| | | | | |
|---|---|---|---|---|
| Telephone | : | (012) 395-8457 | | Enquiry Mr G J Wissing<br>Cluster: Legal Services |
| Fax | : | (012) 395 - 8469 | | Private Bag X828<br>PRETORIA, 0001 |
| E-mail address | | wissing@health.gov.za | Reference | C10/26 |


Ms Eldinah Hwengwere
Faculty of Pharmacy
Rhodes University
PO Box 94
GRAHAMSTOWN
6140

Dear Ms Hwengwere

**NOTICE OF DECISION ON INTERNAL APPEAL: SECTION 77(4) OF THE PROMOTION OF ACCESS TO INFORMATION ACT, 2000 (ACT NO 2 OF 2000)**

1. Your Notice of Internal Appeal, dated 6 September 2011, has reference to the matter.

2. After due consideration of the internal appeal, the relevant authority (the Minister of Health) decided to dismiss the appeal terms of sections 45 and 36 of the of the Promotion of Access to Information Act, 2000 (the Act ), with regard to access to the requested records.

3. The reason for the decision is as follows:

4. The Minister concluded that access to the requested records was correctly refused in terms of section 45 (b) and section 36 of the act and is of the opinion that it would be completely unreasonable for the MCC to have to go through each and every dossier to answer (1) in your original request.

5. Regarding your comments in respect of section 46 of the act, your motivation failed to prove the following:

   (a) The disclosure of the record would reveal evidence of –

   (i) a substantial contravention of, or failure to comply with,the law;, or

   (ii) an imminent and serious public safety or environmental risk; **and**

   (b) the public interest in the disclosure of the record clearly outweighs the harm contemplated in the provision in question.

6. With regard to (2) in your original request, the Minister agrees that the information you requested falls within the ambit of section 36 of the act.

7. If you are aggrieved by the decision taken on the internal appeal, you may, within 180 days, lodge an application with a court against the decision of the internal appeal.

8. We trust that you find the above in order.

**DEPUTY INFORMATION OFFICER**
**DATE:** 21/10/11

# Appendix 13: MCC PAIA Manual request

Faculty of Pharmacy
Rhodes University
P.O. Box 94
Grahamstown, 6140

25 October 2011

Deputy Information Officer

Private Bag X828

Pretoria, 0001

***Our ref: 0001/MCC/2011***

Dear Mr Wissing

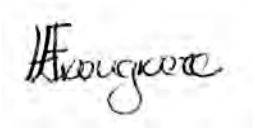
**RE: ACKNOWLEDGEMENT OF DECISION OF INTERNAL APPEAL**

I would like to acknowledge and thank you for the response I received from you dated 21 October 2011. The decision to refuse the request in terms of Section 45(b) and Section 36 of the Promotion of Access to Information Act, (Act 2 of 2000) has been noted.

As a follow-up, I would like to enquire about the second part of the request I made in the Internal appeal which was regarding a request for a copy of the MCC's Information Manual (which is required to have been compiled in terms of Section 14 (1) of the Promotion of Access to Information Act, (Act 2 of 2000). Please may I have the copy sent to me electronically at: g06h3782@campus.ru.ac.za

I look forward to your response.

Kind regards



Eldinah Hwengwere